A RANDOMISED OPEN LABEL COMPARATIVE STUDY OF HYDROXYCHLOROQUINE WITH BETAMETHASONE ORAL MINIPULSE IN THE MANAGEMENT OF PATIENTS WITH ALOPECIA AREATA

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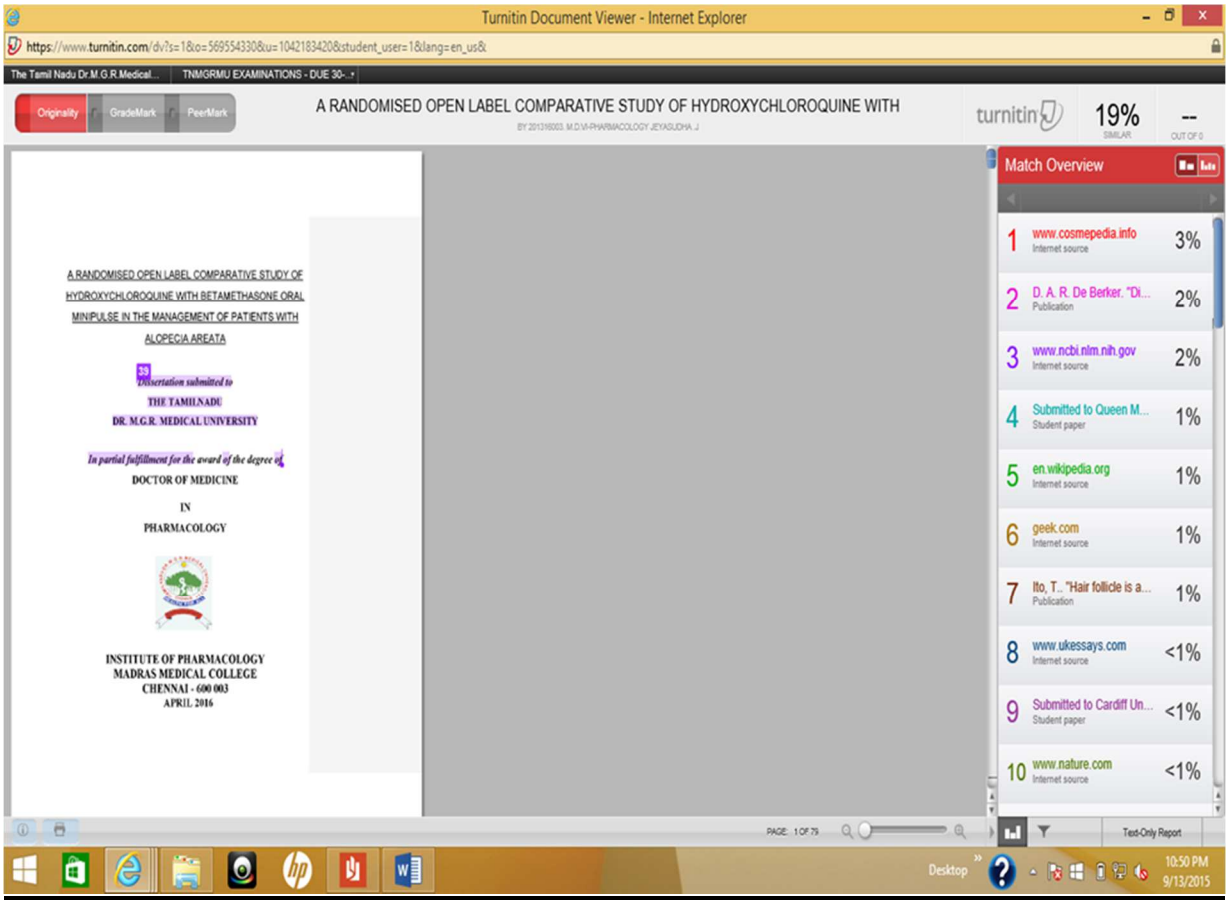
TURNITIN ANTI-PLAGIARISM SOFTWARE – CERTIFICATE



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A RANDOMISED, OPENLABEL COMPARATIVE STUDY OF HYDROXYCHLOROQUINE WITH BETAMETHASONE ORAL MINIPULSE IN PATIENTS WITH ALOPECIA AREATA

AUTHORS: *Dr. J.Jeyasudha, Dr. K.M.Sudha, M.D,* Institute of Pharmacology, Madras Medical College.

ABSTRACT

AIM:

To compare the efficacy and tolerability of Hydroxychloroquine with standard Betamethasone oral minipulse in the management of Alopecia areata.

METHODOLOGY:

This was an open label, comparative, randomized, prospective study. 60 patients with Alopecia areata, were included and randomized into two groups of 30(male-18, female-12) each. Control group received Tab. Betamethasone 5mg/day on two consecutive days of week for 12 weeks and Study group received Tab. Hydroxychloroquine 400 mg/day for a period of 12 weeks. They were followed-up for another 12weeks. Scale of Alopecia Tool score, Dermatology Life Quality Index and Global assessment were used to assess the severity of hair loss, impact on quality of life and treatment outcome respectively. The tests were done every 4 weeks and lab investigations were done at baseline and at the end of 12 weeks.

RESULTS:

94 patients were screened and 60 patients were included. All patients completed the study. At the end of 12 weeks, there was a statistically significant reduction in SALT and DLQI scores in both control and Study groups. But during the follow up period, the study group showed an increase in the scores compared to the control group. Relapses were more in the study group. No significant difference in the incidence of adverse events was noted between the two groups. No differences in laboratory parameters were observed from baseline to 12 weeks.

CONCLUSION:

Hydroxychloroquine 400 mg/day is efficacious and safe in the management of Alopecia areata.

KEY WORDS:

Betamethasone oral minipulse, Hydroxychloroquine, Alopecia areata.

INTRODUCTION

Alopecia areata is a chronic disease which affects the hair follicle and the nails. Both genetic and environmental factors play a role in the pathogenesis of the disease. Alopecia areata is associated with atopy and other autoimmune diseases like myxoedema and pernicious anaemia.[1] Stress is also a known precipitating factor.

The onset of the disease usually occurs in the second decade, although any age may be affected. Both males and females are equally affected. The usual presentation is an asymptomatic patch of loss of hair, which may occur on the scalp or any other hairy part of the body. Eyebrows and eyelashes may be involved. Severe cases are characterized by loss of hair on the entire scalp or even the whole of the body[2] .The extensive hairloss gives rise to poor self-esteem and impairment of social and recreational activities. It eventually leads to considerable anxiety and depression in the affected patients.

Histopathology of Alopecia areata shows it to be a T cell mediated autoimmune disorder with antibodies directed against unknown antigens in the hair follicle.[3]This autoimmune process truncates the anagen phase of the hair follicle and diverts it to telogen phase. 34–50% of patients will recover within 1 year, whereas 14–25% have progressive disease, from which full recovery is unusual (less than 10%) [4]. In mild cases, a wait and watch policy may be adopted whereas in very severe and progressive disease, patient should be counselled about using a cosmetic camouflage like a wig.

Treatment of this condition is mainly aimed at arresting the autoimmune process. This is mainly done by topical agents which act by diverting the inflammatory infiltrate away from the hair follicle or by using systemic drugs which suppress the immunity like steroids or other immunosuppressants. But all these modalities of treatment are associated with significant adverse effects in the long term. This makes the patients poorly compliant to therapy and worsens the outcome of the disease. Hence there is a search for a therapeutic agent which alters the immune function without causing major side effects.

Hydroxychloroquine is an antimalarial drug, with T cell modulating function. It is used with varying degrees of success in Rheumatoid arthritis[5] Systemic Lupus Erythematosus and skin conditions like frontal fibrosing alopecia, pseudopelade of Brocq and lichen planopilaris.[6] It is also used as a systemic sunscreen in photodermatoses. There are case reports of successful use of hydroxychloroquine in severe and treatment resistant cases of Alopecia areata from the western countries, but no data are available from India.[7]

Hence this study is undertaken to assess the safety and efficacy of Hydroxychloroquine in Alopecia areata and its tolerability in Indian patients. It is compared with Betamethasone Oral Minipulse (OMP) therapy which is the standard treatment given in this condition.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Alopecia areata is an inflammatory disease of chronic nature mainly affecting the hair follicle and the nails. It was first described by Cornelius Celsus, and the term was coined by Sauvages .The term alopecia means 'fox mange', denoting loss of hair. The incidence is 0.1–0.2% with a 1.7% lifetime risk of developing the disease. In India, the incidence of the disease is 0.7% in the dermatology Outpatient Department.[8] It occurs at all ages. Males and females are equally affected. Both genetic and environmental factors play a role in causation of this condition.

GENETIC FACTORS:

10 to 20% of patients with alopecia areata give a positive family history. There is a 55% concordance in monozygotic twins and no concordance in dizygotic twins. The inheritance of Alopecia areata is polygenic. It is strongly associated with genes of the major histocompatibility complex (MHC), particularly the Class II alleles HLA-DQB1*0301 and HLA-DRB1*1104[9,10]. The susceptibility to Alopecia areata is determined on chromosomes 10, 16 and 18.

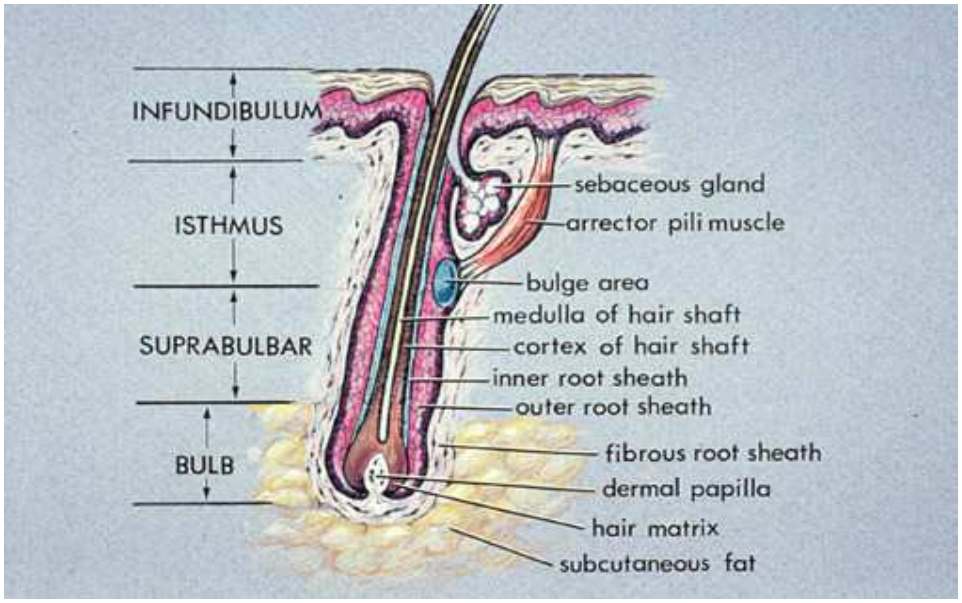
ENVIRONMENTAL FACTORS:

Evidence suggests that in genetically susceptible individuals, environmental factors like trauma, stress, certain diets, vaccination and infection precipitate the hair loss.

Especially, psychological stress is recognized as a triggering factor by many patients. These factors trigger the onset of the disease, but have no role in the final outcome and prognosis.[11]

ANATOMY OF THE HAIR:

In humans, there are three types of hair- Lanugo hair, which is a prenatal coat of fine, soft, unmedullated and unpigmented hair, Vellus hair, which is soft, short , unmedullated, unpigmented hair; and Terminal hair, which is longer, coarser, medullated and pigmented. Before puberty, terminal hair is normally seen in the scalp, eyebrows and eyelashes. After puberty, secondary sexual 'terminal' hair develops from vellus hair in the axillary and pubic areas in response to androgens. The average density of scalp hairs is 1135/cm^2 for newborn, 615/cm^2 for 20-30 years, 485/cm^2 for 30-50 years and 435/cm^2 for 70-80 years. Asians and African Americans have a lower than average scalp hair density.



Anatomy of hair follicle

The hair follicle is divided into 4 parts- the bulb, the Suprabulb region, the Isthmus and the Infundibulum.

Bulb- The bulb includes the dermal papilla and the hair matrix. The dermal papilla consists of mesenchymal cells surrounded by ground substance which is rich in acid mucopolysaccharides (AMPs). The papilla is responsible for hair growth. The lower part of the dermal papilla is connected to the fibrous root sheath. The hair matrix gives rise to the hair shaft and the internal root sheath. In individuals with dark hair, melanin is found within the melanophages of the dermal papilla. Melanocytes can be found between the basal cells of the hair matrix. Melanin is transferred from these melanocytes into the cells that make up the hair shaft and it is responsible for giving color to the hair.

Suprabulb region- The suprabulb region extends from the bulb to the isthmus and consists of hair shaft, IRS, ORS, vitreous layer, and fibrous root sheath.

Isthmus- The isthmus extends from the attachment of the arrector pili muscle (bulge region) to the entrance of the sebaceous gland duct.

Infundibulum- The infundibulum is the upper portion of the hair follicle, above the entry of the sebaceous duct. It is lined by epidermis.

The cut section of the hair follicle shows the following layers from within to outside-

Hair shaft-The hair shaft consists of 3 layers. The outermost layer of the hair shaft is the cuticle which consists of overlapping cells arranged like shingles. The middle layer is the

hair cortex which constitutes the bulk of the hair and consists of cells that keratinize gradually as they move upward from the hair matrix. The innermost layer, medulla is difficult to visualize as it is discontinuous and absent in many regions.

Inner root sheath - The inner root sheath (IRS) is closely apposed to the hair shaft and consists of 3 concentric cell layers.

Outer root sheath- The outer root sheath (ORS) covers the IRS. It extends upward from the matrix cells at the lower end of the hair bulb to the point of entrance of the sebaceous duct. The ORS is thinnest at the level of the bulb and thickest in the middle portion of the hair follicle. It does not keratinize below the level of the isthmus

Fibrous root sheath- The fibrous root sheath is the outermost layer of the hair follicle and consists of thickened collagen bundles which coat the hair follicle. The root sheath is continuous with the dermal papilla at its lower end and with the papillary dermis above it.

THE HAIR CYCLE:

The hair goes through three phases of development known as the anagen, catagen, and telogen phases. Each strand of hair on the human body is at its own stage of development. At any given time all three phases of hair development may be seen in the scalp. The anagen phase is the growth phase of hair. The longer the hair is in the anagen phase, the longer it grows. At any given time, about 85% of the hairs on scalp are in the anagen phase. The catagen phase is also known as the transitional phase .This phase lasts about two weeks. The hair follicle shrinks due to disintegration, the papilla detaches and

cuts the hair strand off from its nourishing blood supply. Ultimately, the follicle shrinks to 1/6 its original length, causing the hair shaft to be pushed upward. During the telogen or resting phase, the follicle remains dormant for 1–4 months. 10-15% of the hairs on one's scalp are in this phase of growth at any given time. Then the hair base breaks free from the root and the hair is shed. A new hair shaft begins to emerge within two weeks.

IMMUNOLOGY OF ALOPECIA AREATA:

Association with other autoimmune disorders:

Alopecia areata is associated with other autoimmune disorders like myxoedema and pernicious anaemia. Circulating autoantibodies to hair follicle tissue have been found in patients, but their role in pathogenesis is not clear. Patients have an increased frequency of circulating organ-specific autoantibodies compared with normal subjects. Nonspecific abnormalities in peripheral T-cells have also been noted. Gilhar et al first showed that hair growth recovered in bald skin transplanted on to athymic nude mice[12]. They also induced alopecia in grafted skin by injecting autologous T cells incubated with hair follicle extracts and antigen presenting cells.

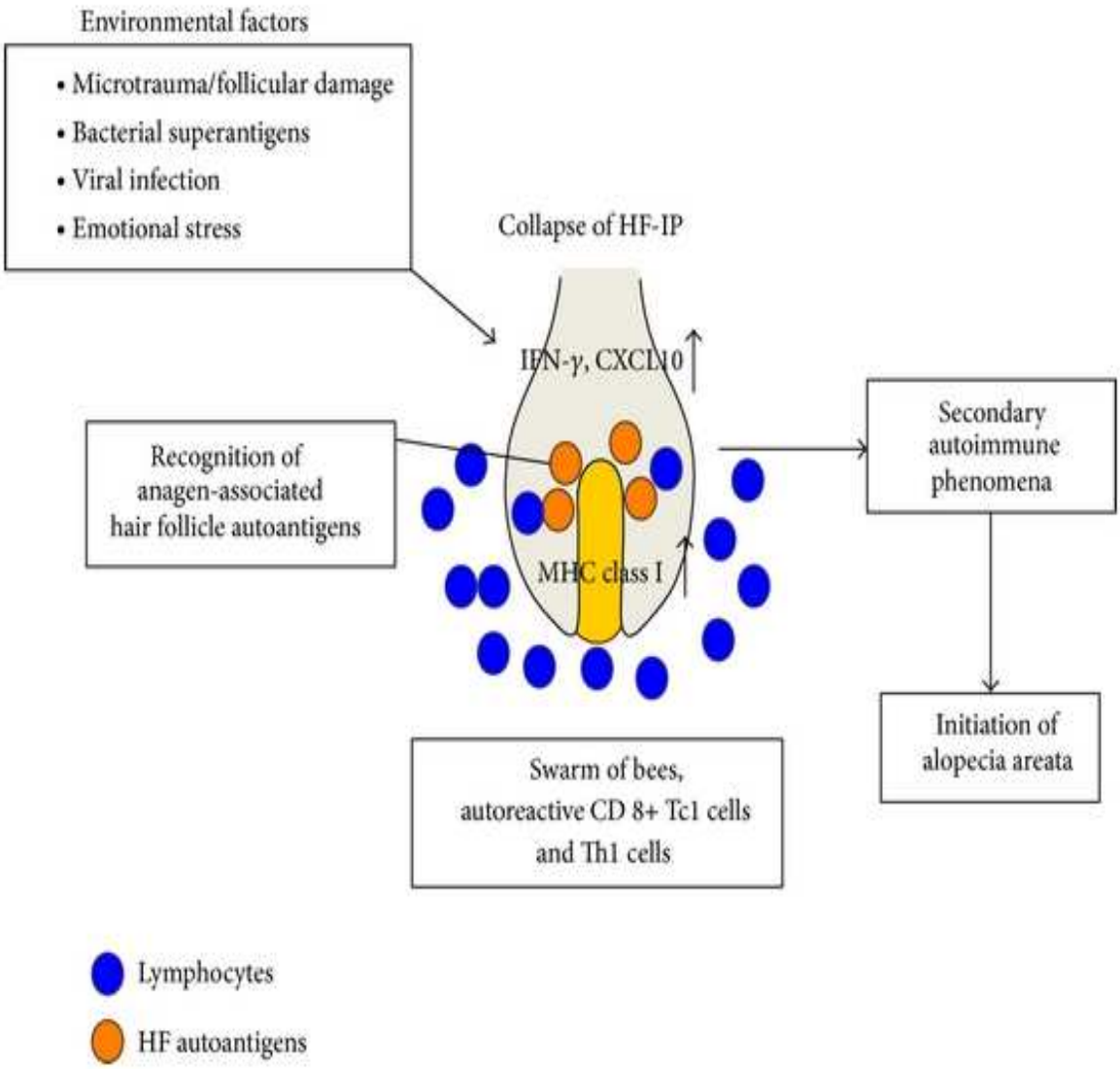
Collapse of Hair follicle Immune Privilege[41]

Certain sites of the body are specially protected from immune reactions, which is termed as Immune privilege. The sites which enjoy immune privilege include anterior eye chamber, parts of testis and ovaries, adrenal cortex, parts of the central nervous

system enclosed by the blood-brain barrier and the placenta. The immunosuppressive milieu prevalent at these sites protects the organs from deleterious immune reactions and loss of function. For example a dangerous immune reaction in the anterior chamber of eye can cause blindness. The anagen hair follicle enjoys Immune privilege due to-

- Absent or barely detectable MHC class I in the outer root sheath and matrix.
- Hair follicular melanocytes of the human anagen scalp are MHC class I-negative.
- Downregulation of the MHC class I pathway-related molecules β 2-microglobulin and transportation of antigen processing-2 (TAP-2).
- Downregulation of interferon regulatory factor-1 expression.
- Upregulation of immunosuppressive factors like TGF- β1 and TGF- β2, ACTH, α-MSH.
- Absence of MHC class II+ or NLDC-145+ Langerhans cells.
- Sparse distribution of NK cells and CD4+ and CD8+ T cells.
- Absence of lymphatics.

HFIP is present during anagen but is lost during the telogen and catagen phases of the hair cycle. Collapse of HFIP contributes to the development of AA, in which pigment-producing anagen hair bulbs are attacked by inflammatory cells. Infections, trauma and stress are known to cause increased production of Interferon-gamma. Interferon (IFN)-γ is a key cytokine implicated in the pathogenesis of AA and it upregulates MHC class I expression in hair follicles.



CD8+ T cells react to autoantigens by binding to MHC class I molecules. These CD8+ T cells accumulate within and around the anagen hair bulbs and initiate the autoimmune process.

CLINICAL FEATURES:

Alopecia areata usually presents at any age and equally affects both sexes. Early onset and positive family history indicate a severe and progressive disease. Ikeda classified Alopecia areata as follows-

Atopic type: It begins early in childhood and most commonly (30-75%) progresses to Alopecia Totalis (AT).

Autoimmune type: It is seen in middle-aged groups and associated with other autoimmune diseases like diabetes mellitus. 10-50% progress to AT.

Prehypertensive type: This is seen in young adults whose parents have hypertension.

Common type: It affects adults aged 20-40 years and AT develops in 5-15% of cases.

Alopecia areata

Nail changes

The initial lesion is a circumscribed, totally bald, smooth patch on the scalp (90%) or any other part of the body (10%). It is asymptomatic and usually noticed by a hairdresser or friend. The patches are devoid of redness, itching, scaling or follicular changes. Individual patches may expand circumferentially, coalesce and form a large patch. Characteristic 'exclamatory mark hairs' are seen either within or at the border of the patches. These are fractured and short hairs with broad distal ends and proximal tapering close to scalp. They are due to hair follicle damage in anagen followed by a rapid transformation to telogen. The presence of exclamatory hairs at the border and the hair pull test with 6 or more hairs from the periphery indicates that the disease may be active. Regrowth is fine and unpigmented initially, but the hairs gradually resume their normal calibre and colour.

Oophiasis

Linear type

In patients with mixture of dark and grey hairs, the disease selectively affects the dark hairs leading to their loss. The unpigmented hairs are spared, which the patients describe as ‘going grey overnight’. Although the white hairs are spared initially, they are not immune and are affected as the disease becomes progressive.[13] The various terms used to describe the patches of alopecia areata are as follows.

ALOPECIA TOTALIS- involves the entire scalp and some body hair such as eyebrows, eyelashes, beard, axillary hair and pubic hair.

ALOPECIA UNIVERSALIS- involves loss of total scalp and body hair.

OOPHIASIS- means ‘snake like.’ It is a band-like hair loss along the posterior occipital and temporal margins.

SISAIPHO- This is also known as oophiasis inversus and presents with alopecia involving the frontal, temporal, and parietal scalp but spares hair along the scalp periphery. This should be differentiated from Androgenetic alopecia.

RETICULAR –The hair loss occurs in a reticular or net like pattern.

PERINEVOID- alopecia patches are seen around the nevi.

LINEAR- hair loss occurs in a linear distribution.

DERMOSCOPY:

Dermoscopy is an easy bedside technique used to observe the severity of hair loss. It can also give a clue to the cause of hair loss. Dermoscopy done on the scalp and hair is known as Trichoscopy. Yellow dots, black dots, broken hairs, tapering hair

(exclamation marks), and short vellus hairs are the characteristic dermoscopic features of Alopecia areata.[14,15] Inui et al. described coudability hairs which are normal looking hairs, but show a thinning and kinking in the proximal aspect. Presence of black dots, broken hair, and tapering hair suggest active disease. There is no single feature in dermoscopy which is diagnostic of Alopecia areata, but a combination of features help to make a proper clinical diagnosis.

NAIL CHANGES:

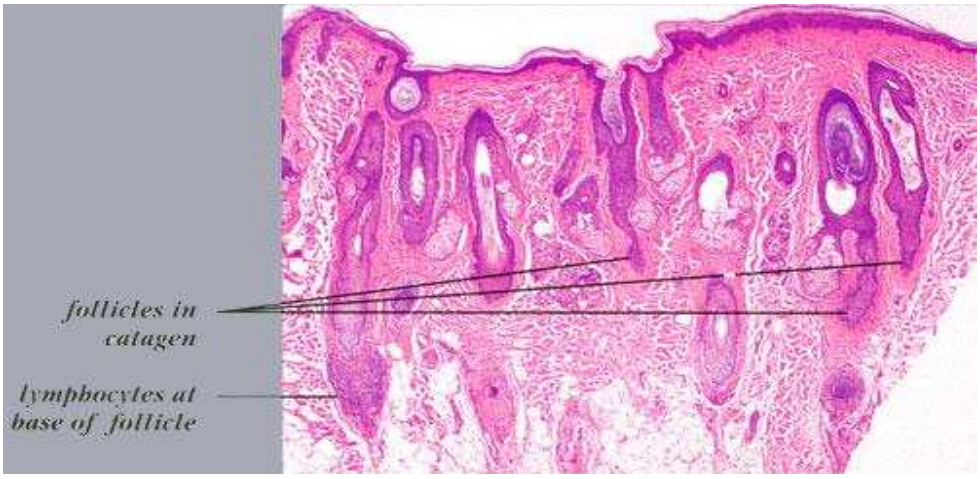
Nail changes are seen in 10-15% of cases of alopecia areata. Nail changes may precede or follow the hair loss, and they may be observed in one or most nails. Sometimes they may be the reason for the patient approaching a dermatologist. The most common finding is a fine, stippled pitting of the nails. Alopecia areata may also cause roughening of the nail plate (trachyonychia) or a non-specific dystrophy. The other changes include Punctate leukonychia, Beau's lines, onychomadesis, mottled and red lunulae.[16] Presence of nail changes indicates a severe disease.

EYE CHANGES:

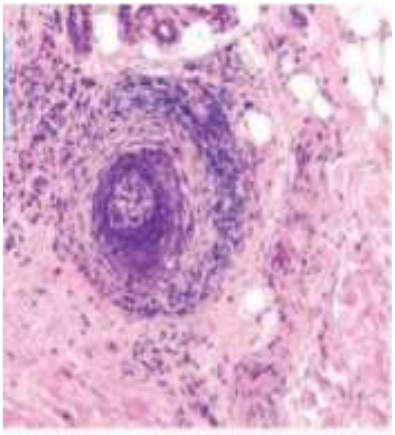
Punctate lens opacities, early cataracts, and fundus abnormalities may occur in 40% to 50% of patients with Alopecia areata.[17]

HISTOPATHOLOGY:

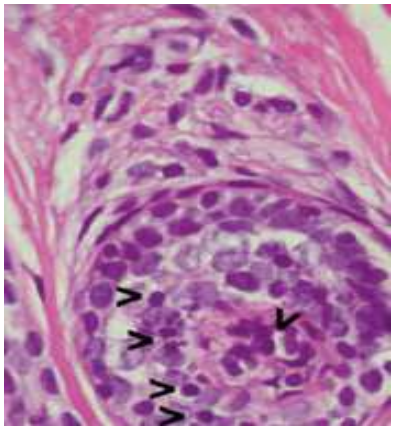
In early stages, the anagen follicles characteristically show a perifollicular and intrafollicular inflammatory cell infiltrate composed of activated CD4 T lymphocytes and an admixture of macrophages and Langerhans' cells. This is termed as 'Swarm of bees' appearance. The infiltrate is seen mainly around the isthmus of the hair follicle which is the site of hair follicle stem cells.



Histopathology of Alopecia areata



Swarm of bees appearance



Lymphocytes within the follicle

Later, anagen follicles are precipitated into telogen. Follicles re-enter anagen but are unable to progress beyond the Anagen 3–4 stage. They then return prematurely to telogen. These cycles of anagen- telogen continue for as long as the disease is active. In chronic cases, there is miniaturization of hair follicle, which loses the hair shaft but may contain remnants of inner root sheath.

PSYCHIATRIC MORBIDITY:

AA is associated with considerable psychiatric morbidity in the form of anxiety and depression. Patchy loss of hair leads to poor self-esteem and impairment in the Quality of Life as evidenced by reduced sports and recreational activities and diminished sexual drive.[18] Colón et al. reported that 74% of patients were given one or more lifetime psychiatric diagnoses based on structured psychiatric interviews. The lifetime prevalence rates of major depression (39%) and generalized anxiety disorder (39%) were high. This shows that patients with AA have a poor Quality of Life (QOL) and are at an increased risk for developing anxiety and depression.

DISEASES ASSOCIATED WITH ALOPECIA AREATA:

Alopecia areata is associated with atopy in 10-22% cases. In these patients, the disease characteristically presents early, is more severe and resistant to treatment. The chance of developing Alopecia Totalis is high (30-75%). It is also seen in association with autoimmune thyroiditis in 8-28% of cases[1]. Other autoimmune disorders

like vitiligo, Addison's disease, Autoimmune polyglandular syndrome are found with Alopecia areata. These patients are more likely to progress to Alopecia Totalis (10-50%). Sharma et al. has reported that vitiligo in family members is an independent risk factor for developing severe forms of alopecia.[19.]Systemic lupus erythematosus, celiac disease, ulcerative colitis, multiple sclerosis are the other associations observed, although the cause for the disease co-occurrence is not known. There is an increased incidence of type I diabetes in the family members of AA, but the AA patients themselves have reduced incidence[20].

DIFFERENTIAL DIAGNOSIS:

Depending on the age, duration of illness and other features, several other conditions should be considered before making a diagnosis. Itchy scaly areas of hair loss in a child may suggest Tinea capitis, while a psychiatric patient with hair loss at accessible sites should prompt a diagnosis of Trichotillomania. Hair loss in secondary syphilis may also mimic Alopecia areata. Sudden acute hair loss may be due to Telogen effluvium and in an adult patient with a large patch over the vertex, a diagnosis of Androgenetic alopecia should be considered. Other common conditions that resemble AA include traction alopecia and Pressure alopecia. When there is doubt, a scalp biopsy is the best aid in diagnosis.

COURSE OF THE DISEASE:

Many cases show a spontaneous regrowth of hair. And some of the treated patients may experience a relapse. For a few patients, the disease runs a remitting relapsing course over several years. A small proportion of patients do not show regrowth even after years of treatment. Poor prognosis is indicated in younger age of onset, positive family history, presence of atopy and autoimmune disorders, disease duration more than one year, severe disease with nail changes, oophiasis pattern hair loss, Alopecia Totalis and Alopecia Universalis.5-10% of patients may progress to total hair loss.

TREATMENT:

Treatment of Alopecia areata ranges from simple reassurance for mild cases, topical agents, systemic therapy to cosmetic camouflage for severe treatment resistant cases.

TOPICAL AGENTS:

These are broadly classified as-

1) Topical Irritants
2) Topical immunomodulators - steroids/ calcineurin inhibitors,
3) Topical Minoxidil
4) Topical contact sensitisers.
5) Other topical agents.

TOPICAL IRRITANTS

These agents cause irritation, a local inflammatory reaction and divert the T lymphocytic infiltrate away from the hair follicle. This effect causes regrowth of hair in the patch. The various topical irritants used include-

- Anthralin
- Dithranol
- Salicylic acid
- Capsaicin gel
- Garlic juice
- Onion juice
- Tincture iodine
- Bexarotene 1% gel
- Tretinoin 0.05% ointment
- Azelaic acid
- Liquid nitrogen cryotherapy.

The efficacy of this treatment is variable. It is also prone to cause severe irritation, folliculitis, regional lymphadenopathy, and staining of skin, clothes, and hair.

TOPICAL STEROIDS:

Topical steroids are the preferred first choice in the treatment of AA because of ease of application, especially in children. The various agents used include Fluocinolone acetonide 0.2% cream, 0.1% betamethasone valerate foam, 0.05% betamethasone

dipropionate lotion, 0.1% halcinonide, 0.05% clobetasol ointment/foam. The efficacy ranges from 28.5 to 61% in various studies depending on the potency of the agent and the duration of treatment.[21]It is recommended to use these drugs 1 cm beyond the affected area. Application of topical steroids under occlusion increases the efficacy and also the incidence of adverse effects. Folliculitis, telangiectasia, striae, purpura, poor wound healing, acneiform eruptions, suppression of HPA axis and skin atrophy are the commonly observed side effects. Topical steroids can be applied on alternate days or 5 days a week to prevent the local side effects.

Intralesional corticosteroids are the treatment of choice for adults in patchy AA. Triamcinolone acetonide is injected into deep dermis or upper subcutaneous tissue using a 0.5-inch long 30-gauge needle at multiple sites, 1 cm apart and 0.1 ml into each site, once in 4-6 weeks. 10 mg/ml concentration is preferred for scalp and 2.5 mg/ml for eye brows and face.[22]The maximum dose should not be more than 20 mg/sitting. Dermal atrophy, Hypopigmentation, telangiectasia can occur. Cataract and glaucoma can occur if intralesional corticosteroids are used near the eyebrows. Hair regrowth starts around 4 weeks with a 60% success rate.

TOPICAL CALCINEURIN INHIBITORS:

Topical calcinuerin inhibitors act by inhibiting transcription following T-cell activation of several cytokines. Topical tacrolimus 0.03% and 0.1% cream and Pimecrolimus 0.1% cream were studied for Alopecia areata. They were found ineffective in this condition.[23,24]Cyclosporine , a calcineurin inhibitor is known to cause Hypertrichosis

by prolonging the anagen phase of hair cycle. A 10% topical preparation of Cyclosporine has been tried for treating Alopecia areata, but the results have not been encouraging. [28]

TOPICAL MINOXIDIL:

Minoxidil causes hair regrowth by stimulating proliferation at the base of the bulb and differentiation above the dermal papilla, besides increasing the vascularity to the scalp. Some authors have reported good hair regrowth in patients with AA. Minoxidil 5% solution is found to be more effective than 2%solution. It is combined with irritants like anthralin or dithranol for a better response.[25]Unwanted facial hair, pruritus and dermatitis are the adverse effects observed. Topical minoxidil is found to be ineffective in alopecia totalis and universalis.

CONTACT SENSITISERS:

These are potential allergens. The patient is first sensitised to these compounds. By repeated application of these compunds, a severe allergic contact dermatitis is induced. This causes immunomodulation and gradual regrowth of hair. Happle proposed that the contact allergen competes for CD4 cells, attracting them away from the perifollicular region (‘antigenic competition’).[26]Other theories include the stimulation of a local T-suppressor-cell response and increased expression of TGF-β in the skin, which causes a suppression of immune response.

The agents used include Dinitrochlorobenzene (DNCB), Diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester (SADBE). DNCB is found to be mutagenic and is

not used these days. Of the other two agents, DPCP is preferred over SADBE as it is cheaper and more stable. The efficacy of both the agents is similar at 50-60%. A 2% solution of DPCP is made by dissolving 20 mg in 1 ml of acetone. The patient is first sensitized with 2% DPCP on a 4 cm^2 area of scalp. It is left on the scalp for 1-2 days to sensitise the patient and then washed. The scalp should be protected from the sunlight when DPCP is applied. Two weeks later, a very low concentration (0.0001%) of DPCP is applied on the same side of scalp and the concentration is increased every week, until a mild erythema and pruritus occur. Once the allergic reaction is established, weekly application of the same concentration is continued and left for 48 hours. Treatment is continued on the same half of the scalp until full regrowth of hair occurs and the second half is treated later. Once hair regrowth is stable for more than 3 months, the treatment is gradually tapered over a period of 9 months. The commonly seen adverse events include severe dermatitis, Cervical/ Occipital lymphadenopathy, Urticaria, Post inflammatory hyper/hypopigmentation. Rarely depigmentation and vitiligo can also occur.[27] Because of potential teratogenicity, these agents are not advised for pregnant and lactating women. Before initiating therapy, all the potential outcomes are discussed with the patient and an Informed Consent is taken. Personnel handling these agents should wear gloves and protect themselves from sensitization.

OTHER TOPICAL AGENTS:

Latanoprost and bimatoprost are prostaglandin analogues, used in open angle glaucoma and they cause hypertrichosis of eyelashes as an adverse effect. A recent trial

shows a cosmetically acceptable eyelash growth in 45% of the latanoprost-treated group.[29] Bimatoprost has also showed cosmetically acceptable eyelash growth in 43.2% of AU patients.[30] Mild eye irritation and hyperemia are the common side effects noted.

SYSTEMIC AGENTS:

Systemic agents are used in severe cases of Alopecia areata like Alopecia Totalis and Alopecia Universalis. The mainstay of Systemic therapy is Corticosteroids. The other drugs are Immunosuppressants, Biologicals and Phototherapy.

CORTICOSTEROIDS:

Corticosteroids are used in Alopecia areata for their immunosuppressive and anti-inflammatory action. Steroids bind to cytosolic receptors and mediate lymphocyte transcription and translation. This leads to –

- Induction of Lymphocyte and Eosinophil apoptosis.
- Depletion of Langerhans cells in epidermis and dermis.
- Decreased immunoglobulin synthesis by B cells.
- Decreased IL-2 production by T cells.

These effects bring about an immunosuppressive action.[31] They exert their anti-inflammatory effects through the following mechanisms:

- Stabilisation of lysosomal membranes
- Blocking the Phospholipases and inhibiting the synthesis of Prostaglandins and Leukotrienes.

- Decreased chemotaxis of proinflammatory cells.
- Vasoconstriction.

The steroids commonly used for systemic therapy include Prednisolone, Methyl prednisolone, Dexamethasone, Betamethasone, Deflazacort etc. They are administered as tablets or IV injections. When steroids are used long term, they should not be abruptly stopped as they can cause a Rebound Phenomenon. Hence they should be gradually tapered. The common adverse effects of Systemic steroids include electrolyte disturbances, Hypertension, Diabetes, Osteoporosis, Peptic Ulcer, Exacerbation of a latent infection, Psychosis etc. In progressive Alopecia areata, systemic steroids are administered as minipulse therapy.

PULSE THERAPY OF STEROIDS:

Pulse therapy refers to the administration of suprapharmacologic doses of drugs in an intermittent manner to enhance the therapeutic efficacy and reduce the side effects. Pulsed corticosteroid therapy has been proposed as a means of rapidly controlling life-threatening or serious conditions with minimal toxicity, allowing for less aggressive long term maintenance therapy.[32]

The selection of drugs and their dosages is arbitrary and based upon cost and convenience. Conventionally, methyl predinsolone is the agent most commonly used. Pulsed Prednisolone and dexamethasone have made the treatment more affordable and

accessible to patients. Steroid pulse therapy is routinely used for conditions like prevention of renal graft rejection, lupus nephritis, rheumatoid arthritis, pyoderma gangrenosum, pemphigus vulgaris, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, toxic epidermal necrolysis, Steven Johnson's syndrome, sarcoidosis and systemic vasculitis. The side effects are less frequent compared to daily corticosteroid therapy. Side effects peculiar to steroid pulse therapy include hiccoughs, facial flushing, diarrhoea, weakness, joint and muscle pains.[33]The various pulse regimens used for Alopecia areata are-

a. IV Prednisolone 100mg/day for 3 days in a month repeated for 3 courses.[34]
b. Oral Prednisolone 200 mg once a week for 3 months.
c. 1 g of IV methylprednisolone/day for up to 5 days in a month, repeated for 3 courses.

But all these regimens need admission and clinical and laboratory monitoring. Hence minipulse therapy is preferred in Alopecia areata which can be administered in OPD setup.

Oral betamethasone given at a dose of 10 mg once weekly is termed as minipulse. It is used in dermatoses like vitiligo, lichen planus and alopecia areata with variable success rates. 10 mg of betamethasone maybe split into 2 equal doses and given as 5 mg/day on 2 consecutive days of a week.[32]

IMMUNOSUPPRESSANTS:

Cyclosporine A causes hypertrichosis in patients because of prolongation of anagen phase of hair growth cycle. Its use is limited because of side effects and high relapse rate following discontinuation. It is not routinely used in AA.[35]. In a clinical trial Methotrexate showed efficacy in 57% of patients. [36]. Azathioprine when given at a dose of 2 mg/Kg/day showed regrowth in 53% of patients.[37.]

PHOTOTHERAPY:

Psoralens+UVA therapy is found to be effective in AA by decreasing the perifollicular inflammatory infiltrate. A good response to PUVA is reported in 85% of AA patients. PUVA in combination with steroids is found effective in resistant cases of AT and AU.[38]. Mild erythema, burning and increased chance of melanoma are the expected side effects. Fractional Erbium YAG laser has shown complete hair regrowth in a patient who has not responded to conventional therapies.

BIOLOGICS:

Biologics like infliximab, etanercept, adalimumab, and efalizumab have been tried in Alopecia areata but found unsuccessful. Patients reported worsening of AA while on treatment. Abatacept has been found to block T-cell activation in mouse models and has been proposed for further clinical evaluation in this condition.[39]

CAMOUFLAGE:

Camouflage is mainly needed when regrowth is slow, poor or erratic. Hairpieces in the form of wigs, demiwigs, wiglets and cascades are mainly used by women. Synthetic hair fibres may be added to the hair to improve thickness. Men may prefer using toupees or shaving. In case of AA of eyebrows or eyelashes, tattooing may be the preferred camouflage. Camouflage may also be needed by children with Alopecia totalis in whom the psychological needs are to be addressed.[40]

STUDY DRUGS

BETAMETHASONE[42, 43]

Betamethasone has a steroid ring, a hydroxyl group attached to the 21 position (21 hydroxy steroid) and a fluorine atom attached to it.

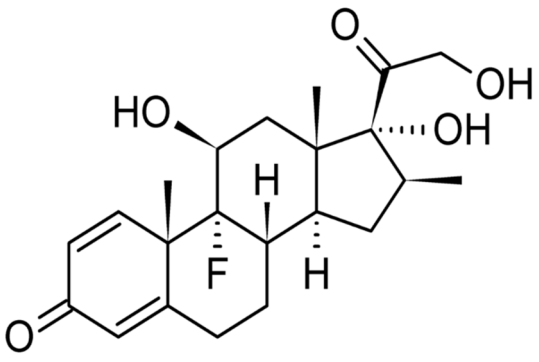
It is a glucocorticoid with minimum mineralocorticoid activity.

Betamethasone is a white, odorless crystalline powder. It is sparingly soluble in acetone and alcohol; slightly soluble in chloroform and ether; and insoluble in water.

Its chemical name is 9alpha-Fluoro-16beta-methylprednisolone.

The molecular weight is 392.46

Its chemical formula is C22H29FO5 and it has the following structure-



Betamethasone

Pharmacological action:

- It exerts anti-inflammatory action by blocking the membrane phospholipases and decreasing the production of Leukotrienes and Prostaglandins which mediate inflammation.
- Its immunosuppressive effect is through apoptosis of lymphocytes and by decreasing the production of IL-2 which is an immune mediator.

Pharmacokinetics:

Absorption:

- It is well absorbed from GIT.
- When administered IV, the peak plasma levels are attained at 10-35 minutes.

Distribution:

- 64% of drug is protein bound.
- It has a high volume of distribution of 75-90 L.
- Plasma half life is 6.5 hours.

Metabolism:

- Extensively metabolized in liver to inactive compounds by CYP3A4

Excretion:

- Mainly in urine, minimally in bile.
- Renal clearance: 9.5 mL/min

Common Indications:

The common indications for using Betamethasone include-

- Adrenocortical Insufficiency
- Adrenogenital Syndrome
- Thyroiditis
- Hypercalcemia
- Rheumatic Disorders
- Dermatologic Diseases
- Allergic Conditions
- Ocular Disorders
- Asthma
- Sarcoidosis
- Antenatal Use in Preterm Labor
- Hematologic Disorders
- Neoplastic Diseases
- Myasthenia Gravis
- Organ Transplants
- Nephrotic and nephritic syndromes
- Carpal Tunnel Syndrome.

Dosage forms:

It is available as oral tablets, injection for IM and IV use, topical preparations and as aerosols for inhalation.

Tablets are available in 0.5 and 1 mg strengths.

Adverse effects:

- Musculoskeletal Effects: Muscle wasting, muscle pain or weakness, delayed wound healing, osteoporosis, aseptic necrosis of femoral head.
- Fluid and Electrolyte Disturbances
- Ocular Effects: Posterior subcapsular and nuclear cataracts, increased intraocular pressure leading to Glaucoma.
- Anaphylactic reactions: Circulatory collapse, cardiac arrest, bronchospasm.
- Nervous System Effects: Euphoria, insomnia, mood swings, depression, personality changes and aggravation of latent psychoses.
- Endocrine and Metabolic Effects: Impaired glucose tolerance, hypercorticism and amenorrhea.
- Immunosuppression
- Increased Susceptibility to Infection

Contraindications:

- Presence of sepsis.
- Immunosuppressive conditions like HIV and TB

- Pregnant and lactating women.
- To be used with caution in diabetics, hypertensives, epileptics and psychotic patients.

Drug Interactions:

- Aminoglutethimide causes loss of corticosteroid-induced adrenal suppression.
- Macrolides cause a decrease in Betamethasone clearance leading to toxicity.
- When Betamethasone is administered concomitantly with drugs like amphotericin B or diuretics, dangerous hypokalemia may be precipitated.
- Concomitant use of anticholinesterase agents and Betamethasone may produce severe weakness in patients with myasthenia gravis.
- Coadministration of Betamethasone and warfarin usually results in decrease in response to warfarin.
- Because corticosteroids increase blood glucose concentrations, dosage adjustments of antidiabetic agents are required.
- Serum concentrations of isoniazid is decreased.
- Cholestyramine increases the clearance of Betamethasone.
- Increased activity of both cyclosporine and Betamethasone occurs when the two are used concurrently leading to convulsions.
- Patients on digitalis glycosides are at increased risk of arrhythmias due to hypokalemia.
- Estrogens decrease the hepatic metabolism of Betamethasone, thereby increasing its effect.

- Drugs which induce hepatic microsomal drug-metabolizing enzyme activity like Phenytoin, Carbamazepine, Rifampicin enhance the metabolism of Betamethasone and cause the dosage to be increased.
- Ketoconazole has been reported to decrease the metabolism of Betamethasone by 60%, leading to an increased risk of side effects.
- Corticosteroids may suppress reactions to skin tests.
- Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response.

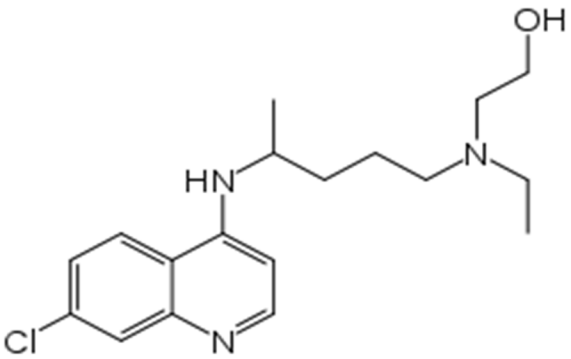
HYDROXYCHLOROQUINE[42,43]

Hydroxychloroquine is an antimalarial drug, which is also being used as an antiinflammatory agent in the treatment of rheumatoid arthritis (Disease-Modifying Antirheumatic Drug).

Its chemical name is 2,4,7 -chloroquinolinyl amino pentyl ethylamino ethanol.

Molecular weight is 335.87.

It is available for oral administration as hydroxychloroquine sulfate 200 mg tablet which contains 155 mg base.



Hydroxychloroquine

Pharmacological actions:

- Hydroxychloroquine increases lysosomal pH in immune cells leading to decreased release of immune mediators. [44]
- It decreases Toll Like Receptor signaling and reduces the activation of dendritic cells and the inflammatory process.

Pharmacokinetics:

Absorption:

- Hydroxychloroquine is readily absorbed from the GI tract.
- Time taken to achieve peak plasma cncentration is 1 to 3 h.

Distribution

- Plasma protein bound
- Hydroxychloroquine is concentrated in the liver, spleen, kidney, heart, lungs, and brain.

Metabolism

- It is partially hepatic.
- Hydroxychloroquine is metabolised by Cytochrome P450 enzymes (CYP 2D6, 2C8, 3A4 and 3A5) to N-desethylhydroxychloroquine.

Elimination

- 50% of the unchanged drug is excreted in urine.
- Renal excretion is increased by acidification of the urine.
- The plasma t ½ is approximately 32 days.

Indications:

- Malaria
- Post lyme arthritis[46]
- Systemic lupus erythematosus, Rheumatoid arthritis, Dermatomyositis, Sjögren's syndrome and Porphyria cutanea tarda.
- Dermatological disorders- Photodermatoses, Lichen planopilaris and other scarring alopecias.

Adverse effects:

- GIT: Reduced appetite, nausea, vomiting, abdominal cramps and diarrhea.
- CNS: Headache, nightmares, convulsions, muscle paralysis, weakness or atrophy.
- SKIN: Worsening of Psoriasis and Porphyria, skin rash, loss of hair, acne.
- EYE: Macular toxicity (related to the total cumulative dose) and Corneal toxicity (Vortex Keratopathy) [45]
- EAR: vertigo, tinnitus, hearing loss.
- OTHERS: blood disorders, liver failure, itching, Urticaria, loss of weight.

Contraindications:

- Pregnant and Lactating women
- Persons with G6PD deficiency
- Patients with preexisting retinopathy.

OBJECTIVES

OBJECTIVE

To evaluate the efficacy and tolerability of Hydroxychloroquine in the management of patients with Alopecia areata compared to weekly oral minipulse therapy with Betamethasone.

PRIMARY ENDPOINT:

- Percentage regrowth of hair in each quadrant of scalp as estimated using Severity of Alopecia Tool.

SECONDARY ENDPOINT:

- Improvement in Dermatology Life Quality Index.

Improvement in Global Assessment Score.

METHODOLOGY

METHODOLOGY

The study was conducted in patients with Alopecia areata of the scalp, attending Outpatient Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai.

Study design:

A randomized, open label, prospective, interventional, comparative study.

Study population:

Adult patients with Alopecia areata of the scalp attending Outpatient Department, Department of Dermatology.

Study center:

Institute of Pharmacology, Madras Medical College & Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai.

Study period:

August 2014 to July 2015.

Study duration:

Treatment period of 12 weeks and

Post treatment follow up period of 12 weeks per patient.

Sample size:

60 patients (Control group - 30, study group - 30).

Eligibility criteria:

Inclusion criteria:

- Age: 18 -60 years
- Sex: Both genders
- Patients with Alopecia areata of the Scalp region.
- Patients willing to give written informed consent.

Exclusion criteria:

- Pregnant women and lactating mothers
- Patients with known hypersensitivity to Hydroxychloroquine
- Patients with visual symptoms or evidence of retinal damage
- Those who have participated in another clinical study in the last three months
- Patients with Diabetes mellitus, Hypertension, HIV infection or any other chronic systemic illness of liver, kidney, gastrointestinal tract, heart etc.

Study Procedure:

The study was conducted after obtaining the approval from Institutional Ethics Committee, Madras Medical College and it was done in accordance with Good Clinical practice (GCP) guidelines.

Patients diagnosed with Alopecia areata attending the Outpatient department, Department of Dermatology, Madras Medical College and Rajiv Gandhi Government General Hospital, were explained about the study purpose, procedure and benefits of the study. Written informed consent was obtained from those subjects who are willing to participate in the study in the prescribed format in regional language. The demographic details of the patients were obtained and recorded.

The subjects were screened by complete medical history, clinical examination and laboratory investigations. Those who fulfilled the inclusion and exclusion criteria were enrolled.

RANDOMIZATION:

The enrolled patients were randomized by simple randomization into either control group or study group and received the respective therapy.

TREATMENT PLAN:

Control group:

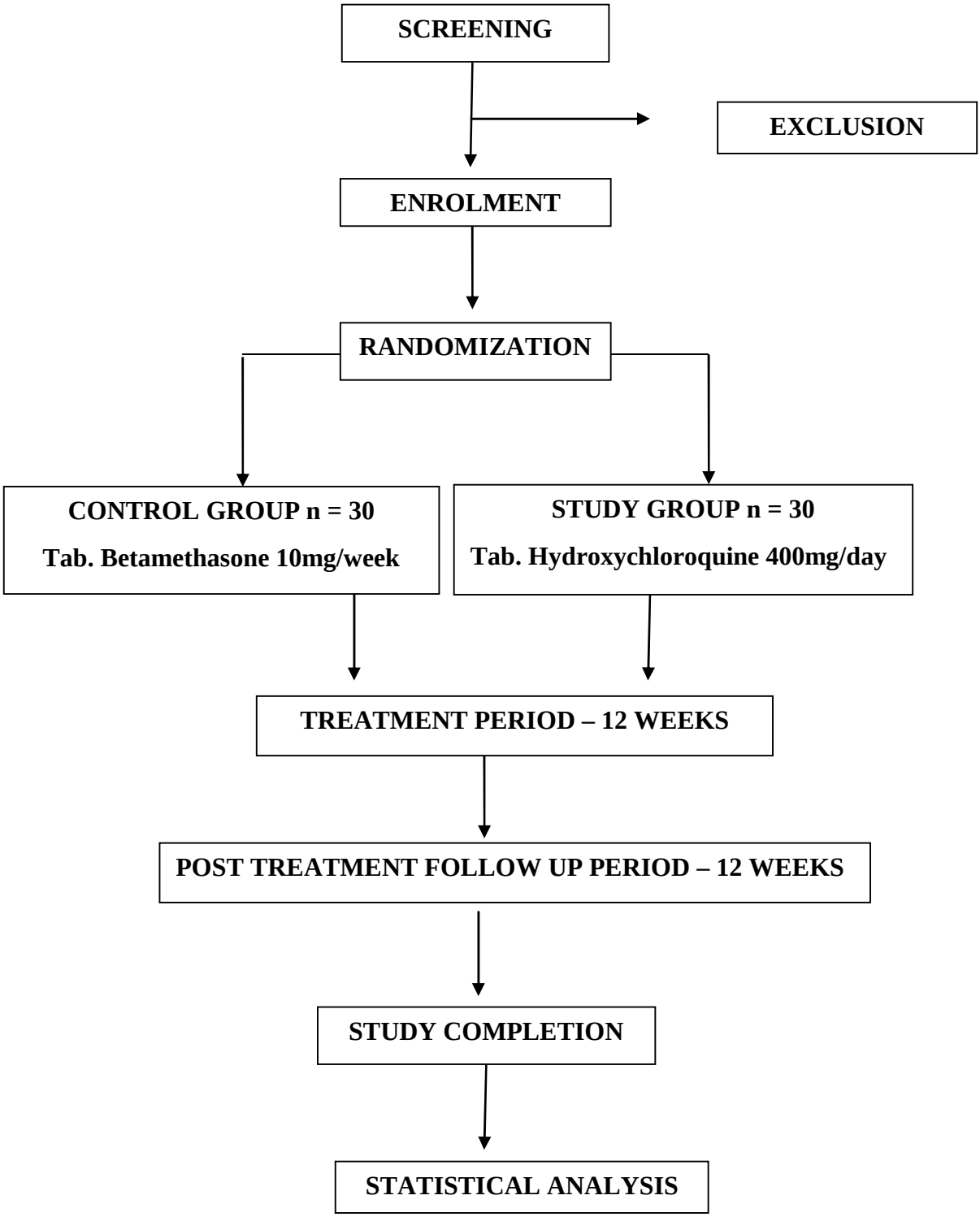
Tab. Betamethasone 5mg on two consecutive days of the week for 12 weeks.

Study group:

Tab. Hydroxychloroquine 400 mg/day for 12 weeks.

After the treatment period of 12 weeks, the drugs were stopped and the patients were followed up for a further 12 weeks.

STUDY FLOW CHART



ASSESSMENT PARAMETERS:

- Hair regrowth on scalp is assessed using Severity of Alopecia Tool (SALT).
- The Psychosocial impact of the disease is assessed using Dermatology Life Quality Index (DLQI).
- Outcome of treatment is assessed using Global Assessment (GA).

SEVERITY OF ALOPECIA TOOL: [47]

SALT score is useful for quantitative assessment of scalp hair loss.

The entire scalp is divided into 4 parts based on the surface area,

Vertex (40% - 0.4),

Occipital (24% - 0.24),

Right profile (18% - 0.18), and

Left profile (18% - 0.18).

Percentage of hair loss in each area is determined independently and is multiplied by the percentage of scalp covered in that area of the scalp, and summing the products of each area gives the SALT score.

For example, if the hair loss is 40%, 30%, 20% and 10% in top, back and right and left side respectively, then the SALT score can be calculated as- $(40 \times 0.4) + (30 \times 0.24) + (20 \times 0.18) + (10 \times 0.18) = 16 + 7.2 + 3.6 + 1.8 = 28.6$.

SALT score is easily reproducible and validated. However, it does not include hair pigmentation and nail involvement. Also the loss of hair in other areas of the body cannot be assessed.

DERMATOLOGY LIFE QUALITY INDEX: [48]

The Dermatology Life Quality Index is the first dermatology-specific quality of life questionnaire. The DLQI consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, and school, personal relationships and treatment over the last one week period. Each question is scored from 0 to 3 and the scores summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). It is designed to be used in adults.

GLOBAL ASSESSMENT:

The treatment outcome and satisfaction level is measured using Global Assessment. The score is given as below-

A) Physician

- Excellent (4)
- Very good (3)
- Good (2)
- Satisfactory (1)
- No Response (0)

B) Patient

- Excellent (4)
- Very good (3)
- Good (2)
- Satisfactory (1)
- No Response (0)

The score is independently given by the physician and patient and the sum is obtained.

INVESTIGATIONS:

The following laboratory investigations were performed in the patients on screening and at the end of treatment period.

- Haematology - Haemoglobin, Total leucocyte count.
- Blood glucose
- Blood urea
- Serum creatinine
- Liver function test (Total Bilirubin, SGOT, SGPT)
- Ophthalmic examination

VISIT 1 (Baseline):

- Written informed consent obtained.
- Randomization done.
- Demographic details obtained.

- Medical history taken and recorded.
- Vital signs recorded.
- SALT, DLQI and GA scores recorded.
- Laboratory investigations done.
- Ophthalmic evaluation done
- Study drugs issued for 4 weeks to respective groups.
- Patients instructed to report if any adverse events occur.

Visit 2(At the end of 4 weeks):

- Vital signs recorded.
- Patients asked to return empty strips to check compliance.
- Clinical examination done.
- SALT, DLQI and GA scores recorded.
- Adverse events monitored.
- Study medication issued for subsequent 4 weeks.

Visit 3 (At the end of 8 weeks):

- Vital signs recorded.
- Patients asked to return empty strips to check compliance.
- Clinical examination done.
- SALT, DLQI and GA scores recorded.
- Adverse events monitored.
- Study medication issued for subsequent 4 weeks**.**

Visit 4 (At the end of 12 weeks):

- Vital signs recorded.
- Patients asked to return empty strips to check compliance.
- Clinical examination done.
- SALT, DLQI and GA scores recorded.
- Adverse events monitored.
- Lab investigations done.
- Ophthalmic evaluation done.

Visit 5 (At the end of 16 weeks):

- Vital signs recorded.
- Clinical examination done.
- SALT, DLQI and GA scores recorded**.**

Visit 6 (At the end of 20 weeks):

- Vital signs recorded.
- Clinical examination done.
- SALT, DLQI and GA scores recorded**.**

Visit 7 (At the end of 24 weeks):

- Vital signs recorded.
- Clinical examination done.
- SALT, DLQI and GA scores recorded.

Follow up:

The patients were followed up every 4 weeks during the treatment period and the post treatment period for assessing the severity of Alopecia areata and for the possibility of recurrence of the disease.

Adverse events:

Patients were advised to report the occurrence of any adverse drug events, other illnesses or intake of other drugs. Any adverse event reported by the patient or observed by the physician during the study was recorded. The onset of the event, causal relationship to the study drug and treatment given were recorded.

Withdrawal:

During the study period the subject was allowed to withdraw his/her voluntary consent and opt out of study. Similarly at the discretion of the investigator, the subjects were withdrawn from the study if any serious adverse events occurred.

Statistical analysis:

The obtained data was analyzed statistically using SPSS software version 21.0. Distribution of age was analyzed by ANOVA and Sex distribution was analyzed by Pearson chi- square test.

The differences within the groups in SALT score, DLQI score and GA were analyzed using students paired t-test. Similarly the differences between the control and test groups were analyzed using independent t-test. For the laboratory investigations, the differences within the groups before and after treatment were analyzed using student's paired t- test.

p value <0.05 was considered to be statistically significant.

RESULTS

RESULTS

This study was conducted to assess the efficacy and safety of Hydroxychloroquine in comparison with Betamethasone oral minipulse in patients with Alopecia areata.

94 patients were screened, of which 28 patients were excluded from the study based on selection criteria and 6 patients who were eligible for the study were not willing to participate.

Thereby 60 patients were enrolled in this study. They were randomly allocated to one of the 2 groups: Control group [30 patients-Betamethasone] and Study group [30 patients-Hydroxychloroquine]. All the enrolled patients completed the study.

STUDY FLOW CHART

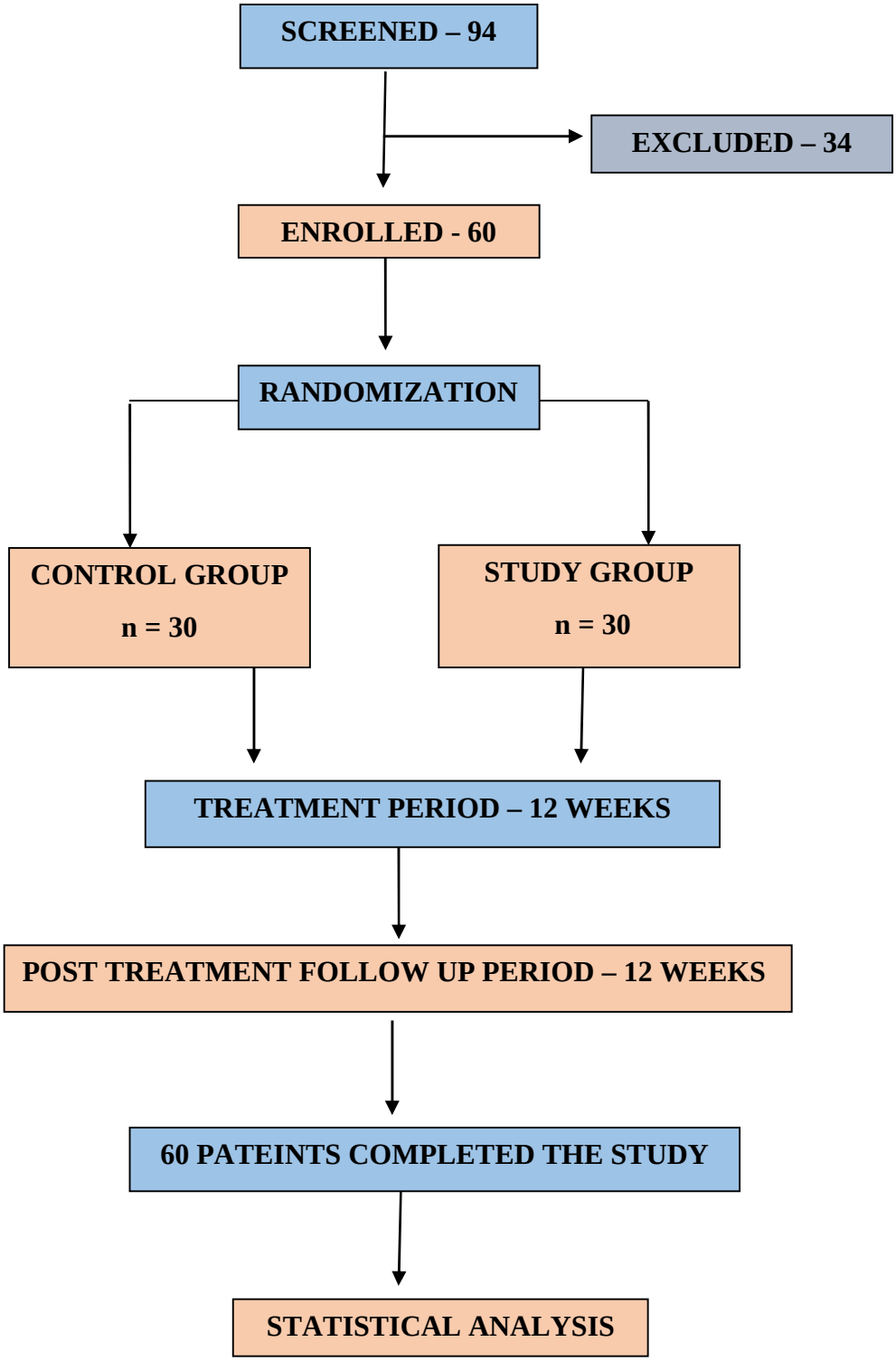


TABLE 1: AGE DISTRIBUTION

AGE(YEARS)	CONTROL	STUDY
18-30 YEARS	**18**	**18**
31-40 YEARS	**6**	**9**
41-50 YEARS	**6**	**3**
TOTAL	**30**	**30**

Table-1 shows the age distribution of patients among the control and study groups. Both treatment groups had more patients in 18 to 30 age group.

FIGURE-1: AGE DISTRIBUTION

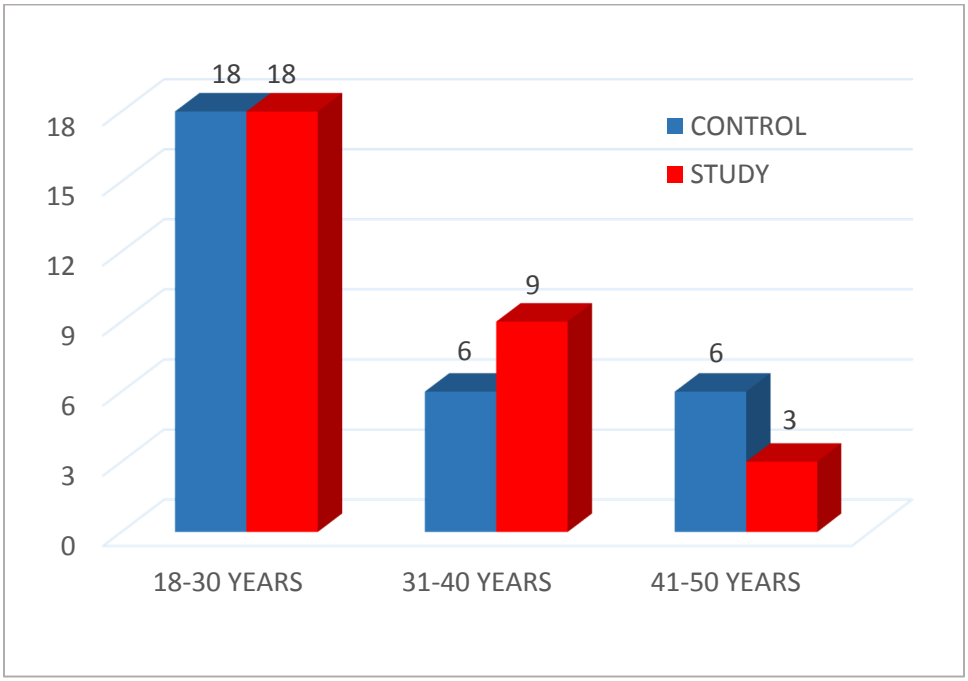


Figure-1 is the graphical representation of table-1

TABLE-2: MEAN AGE DISTRIBUTION

GROUP	NUMBER OF PATIENTS (n)	MEAN AGE IN YEARS	S.D
CONTROL	30	30.3	8.77
STUDY	30	30.5	7.83
P VALUE	0.673		

Table-2 shows the Mean Age Distribution of patients among the control and study groups. The mean age of patients in control group was 30.3years and in the study group was 30.5years.

FIGURE -2 MEAN AGE DISTRIBUTION

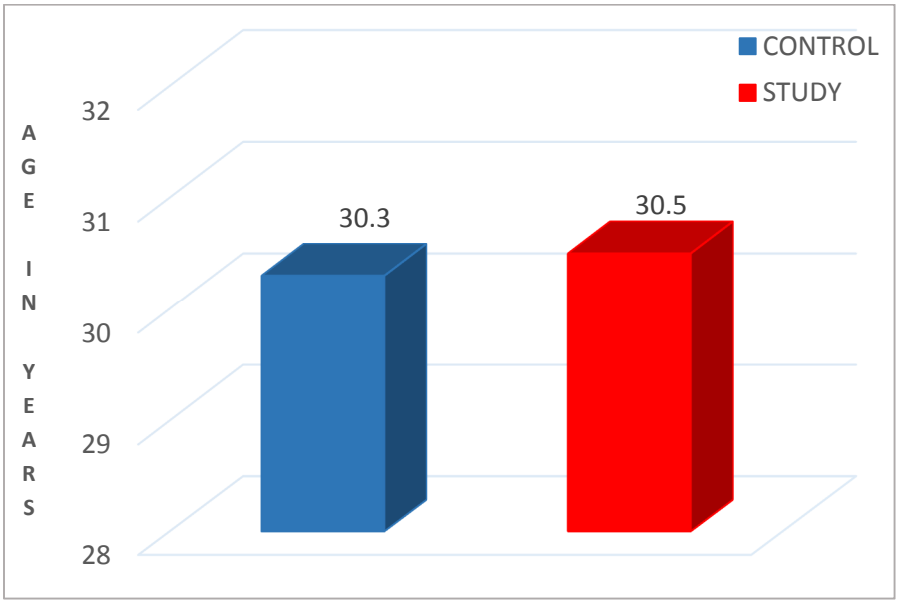


Figure-2 is a graphical representation of Table-2.

TABLE-3: GENDER DISTRIBUTION

GROUP	MALE		FEMALE		TOTAL	
	N	%	N	%	N	%
CONTROL	18	60	12	40	30	100
STUDY	18	60	12	40	30	100

Table 3 shows the gender distribution in the control and study groups.

Percentage of males was higher than females in both the groups.

FIGURE-3: GENDER DISTRIBUTION

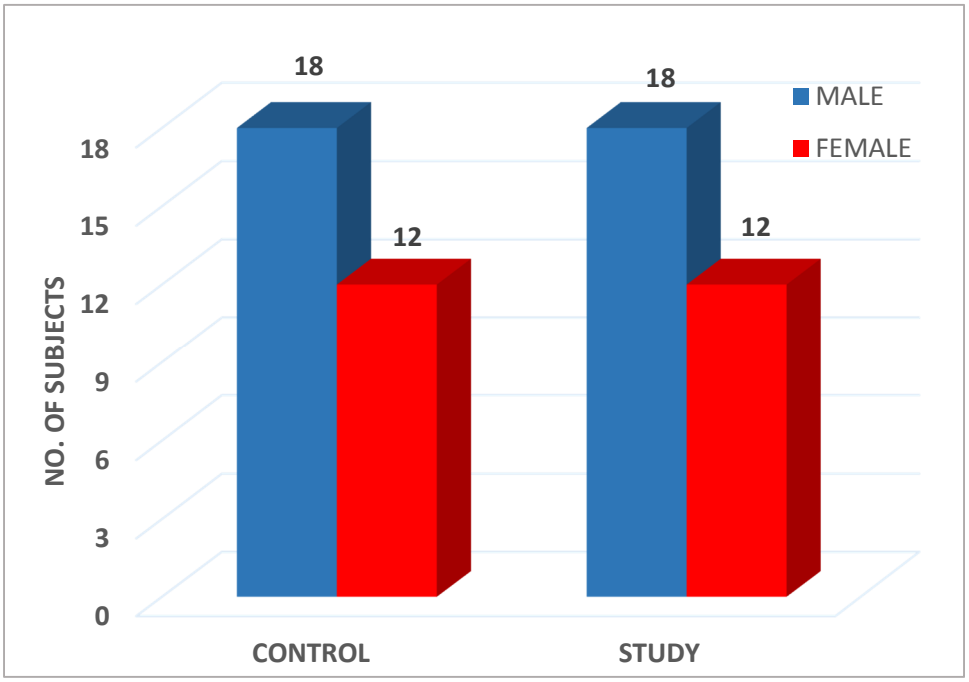


Figure-3 is the graphical representation of Table-3

TABLE-4: NUMBER OF PATCHES OF ALOPECIA AREATA

GROUP	MEAN
CONTROL	2.70
STUDY	2.667
p-VALUE	0.915

Table-4 shows the number of patches of Alopecia areata in both the control and study groups. No significant difference was observed between the groups.

FIGURE-4: NUMBER OF PATCHES OF ALOPECIA AREATA

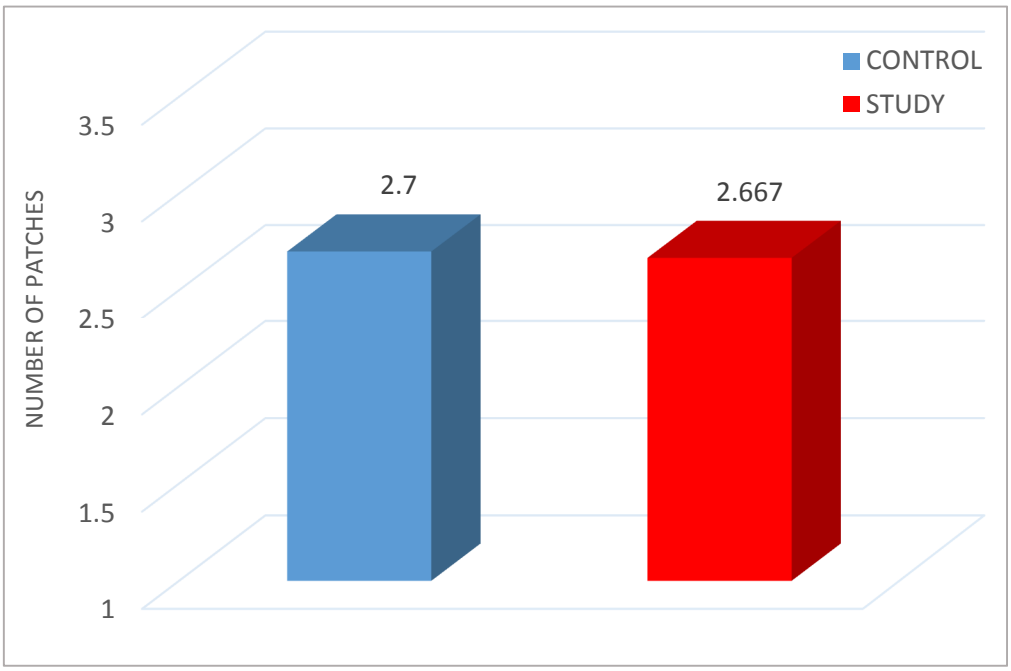


Figure-4 is a graphical representation of Table-4

TABLE 5: DURATION OF DISEASE

GROUP	MEAN (MONTHS)	S.D
CONTROL	5.42	3.24
STUDY	5.87	3.80
P VALUE	0.62	

Table 5 represents the mean duration of the disease. There is no significant difference between the control and study groups.

FIGURE 5: DURATION OF DISEASE

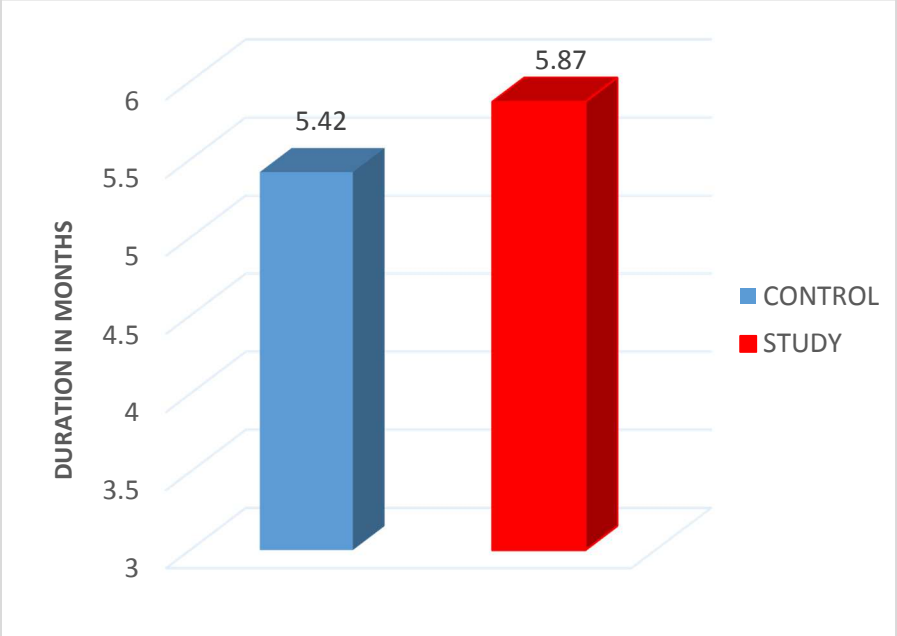


Figure 5 is the representation of Table 5

TABLE 6: SCALE OF ALOPECIA TOOL

DURATION	CONTROL GROUP		STUDY GROUP		P VALUE
	MEAN	S.D	MEAN	S.D	
0 WEEKS	21.50	11.64	22.37	9.08	0.75
4WEEKS	19.80	10.31	22.23	8.79	0.33
8 WEEKS	13.77	6.60	16.6	6.90	0.10
12 WEEKS	9.17	4.94	9.83	4.71	0.59
16 WEEKS	8.13	4.45	9.80	4.41	0.15
20 WEEKS	7.30	4.26	10.0	4.66	0.02
24 WEEKS	7.47	4.48	10.33	5.38	0.03
P VALUE	<0.01		<0.01		

Table-6 shows mean reduction in hair loss in both the groups by SALT score from baseline to week 24.

Intragroup analysis showed a significant decrease in mean SALT score in both the control and study groups from baseline to 24 weeks. Between the groups, the SALT score reduction is similar in both the control and study groups from baseline to 16 weeks. At 20 and 24 weeks, a greater improvement is seen in the control group than the study group.

FIGURE 6: SCALE OF ALOPECIA TOOL

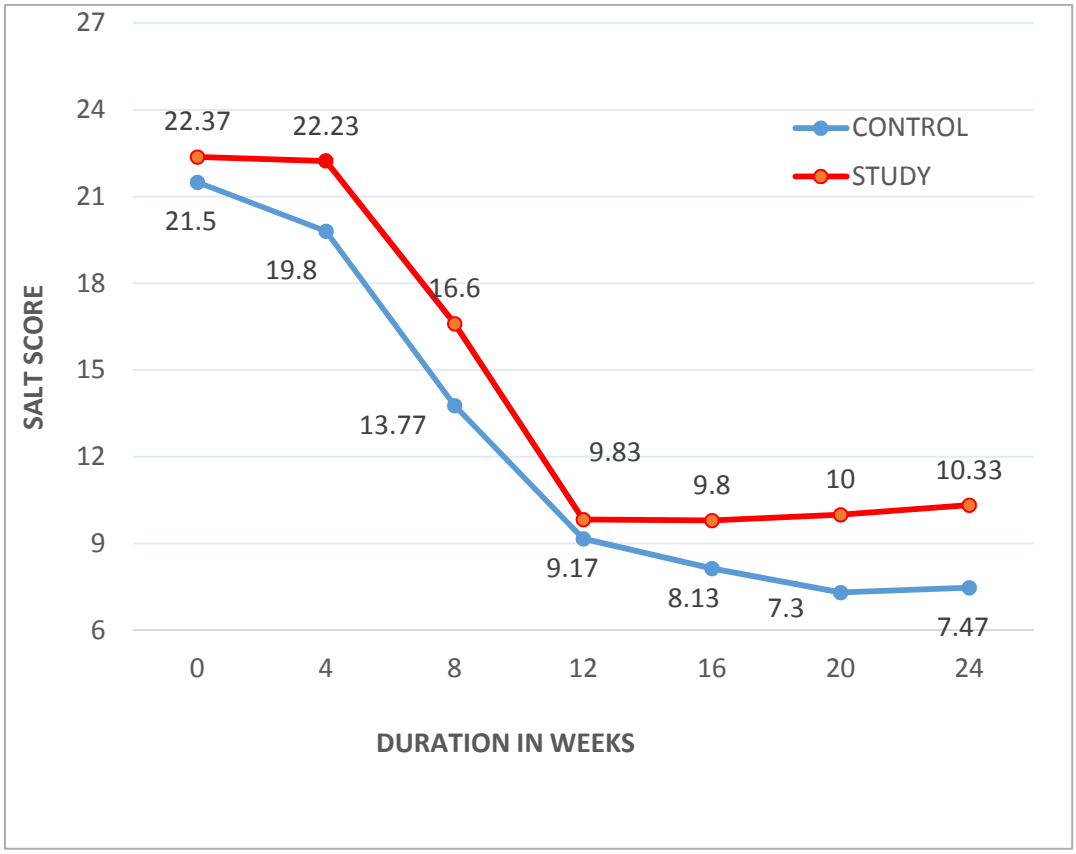


Figure 6 is a graphical representation of Table 6.

TABLE-7: SALT SCORE AT 12 WEEKS

GROUPS	BASELINE		12 WEEKS		P VALUE
	MEAN	S.D	MEAN	S.D	
CONTROL	21.50	11.643	9.17	4.935	<0.01
STUDY	22.37	9.076	9.83	4.713	<0.01
P VALUE	0.749		0.595		

Table 7 shows the mean SALT score of control and study groups at baseline and 12 weeks. Comparison between the groups shows no significant difference in the mean SALT scores at baseline and at 12 weeks.

TABLE-7A: SALT SCORE AT 24 WEEKS

GROUPS	BASELINE		24 WEEKS		P VALUE
	MEAN	S.D	MEAN	S.D	
CONTROL	21.50	11.643	7.47	4.48	<0.01
STUDY	22.37	9.076	10.33	5.94	<0.01
P VALUE	0.749		0.029		

Table 8 shows the mean SALT score of control and study groups at baseline and 24 weeks. Comparison between the groups showed a significant difference in the SALT scores at 24 weeks. The control group showed a lower SALT score at the end of follow up period when compared with the study group.

FIGURE-7: SALT SCORE

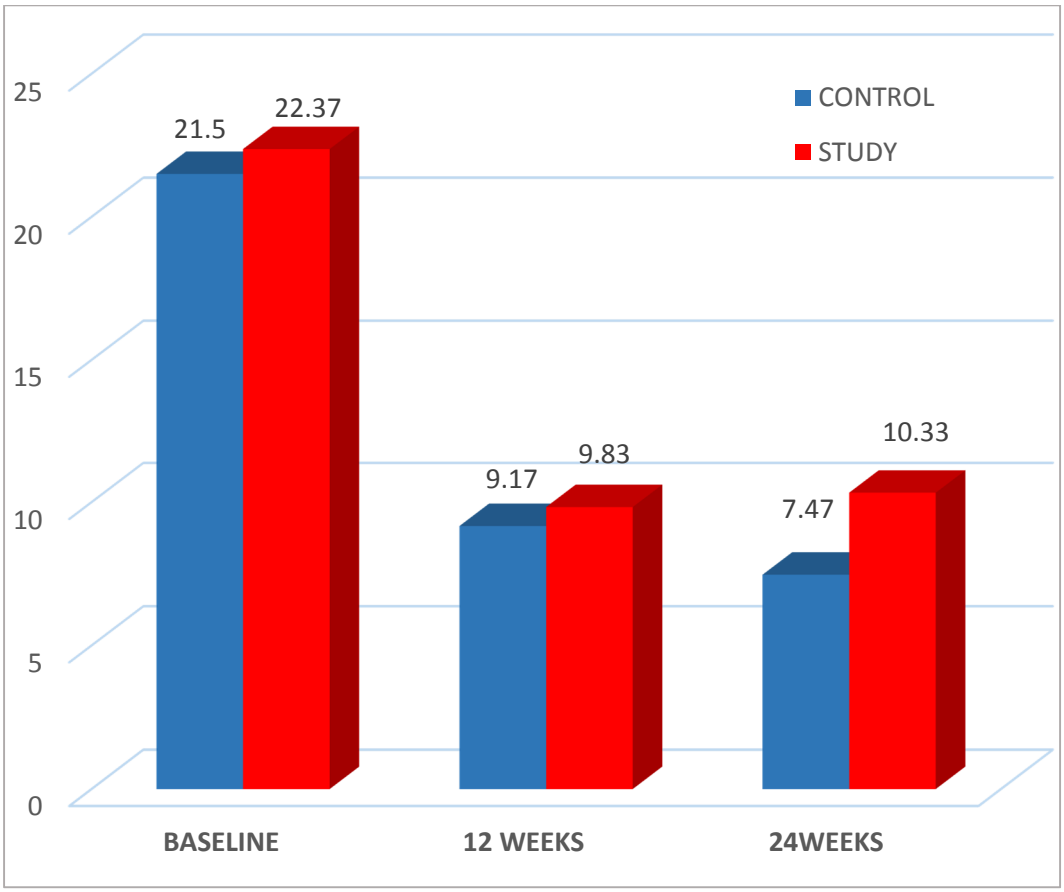


Figure 7 is a graphical representations of Table7 and 7A.

TABLE 8: DERMATOLOGY LIFE QUALITY INDEX

DURATION	CONTROL GROUP		STUDY GROUP		P VALUE
	MEAN	S.D	MEAN	S.D	
0 WEEKS	20.07	3.21	20.53	2.66	0.54
4WEEKS	18.53	3.13	18.87	2.40	0.65
8 WEEKS	15.10	2.45	15.03	2.57	0.92
12 WEEKS	11.90	2.63	12.83	2.88	0.19
16 WEEKS	10.80	2.66	12.23	2.70	0.04
20 WEEKS	11.13	2.84	13.03	3.03	0.02
24 WEEKS	11.53	3.41	13.93	3.13	0.006
P VALUE	<0.01		<0.01		

Table-8 shows the Dermatology Life Quality Index score in both the control and study groups. Within group analysis showed a significant reduction in DLQI scores from 0 to 24 weeks in both the control and study groups. Analysis between the groups showed that from 0 to 12 weeks, both the groups showed a comparable score, but from the 16th week onwards, the control group showed a significantly better score than the study group.

FIGURE 8: DERMATOLOGY LIFE QUALITY INDEX

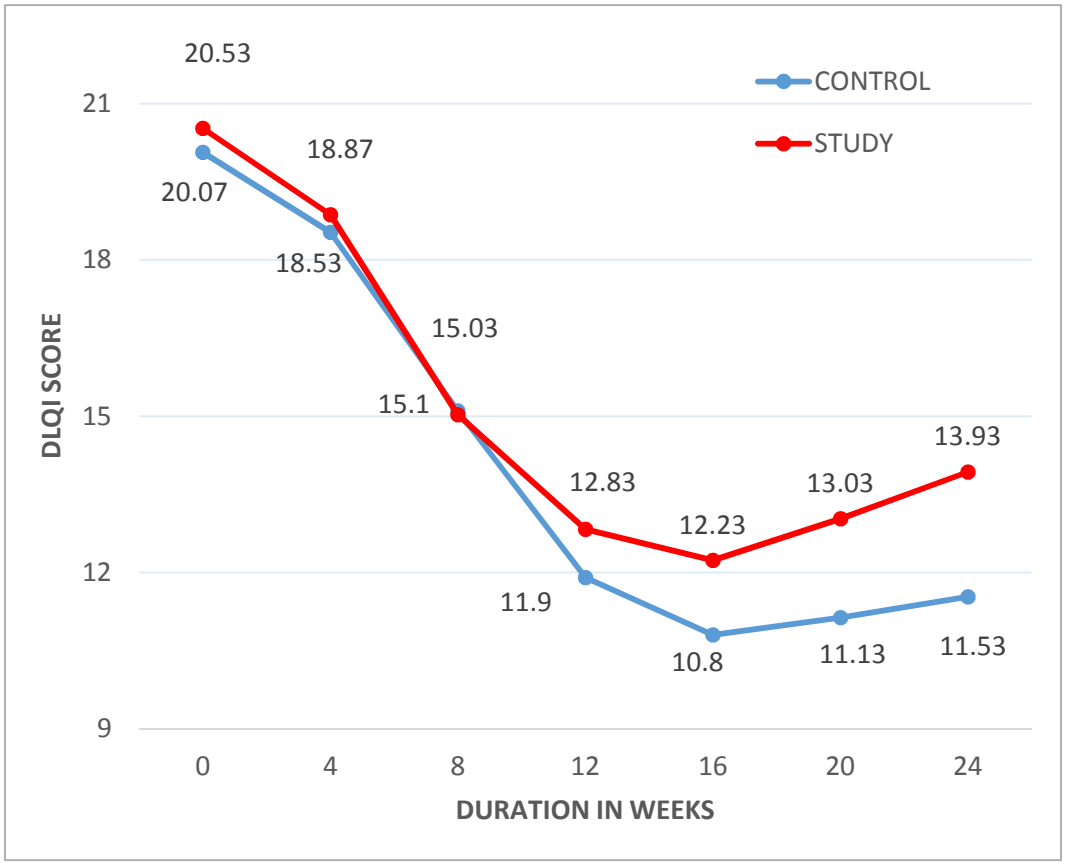


Figure 8 is a graphical representation of Table 8

TABLE-9: DLQI SCORE AT 12 WEEKS

GROUPS	BASELINE		12 WEEKS		P VALUE
	MEAN	S.D	MEAN	S.D	
CONTROL	20.07	3.205	11.90	2.631	<0.01
STUDY	20.53	2.662	12.83	2.878	<0.01
P VALUE	0.542		0.195		

Table 9 shows the mean DLQI score of control and study groups at baseline and 12 weeks. Comparison between the groups showed no significant difference in the mean DLQI scores of the control and study group at baseline and at 12 weeks.

TABLE-9A: DLQI SCORE AT 24 WEEKS

GROUPS			24 WEEKS		P VALUE
		S.D	MEAN	S.D	
CONTROL	20.07	3.205	11.53	3.411	<0.01
STUDY		2.662	13.93	3.129	<0.01
P VALUE	0.542		0.006		

Table 9A shows the mean DLQI score of control and study groups at baseline and 24 weeks. Comparison between the groups showed no significant difference in the DLQI scores at baseline but at 24 weeks, the control group showed a significantly lower score than the study group.

FIGURE 9: DLQI SCORE

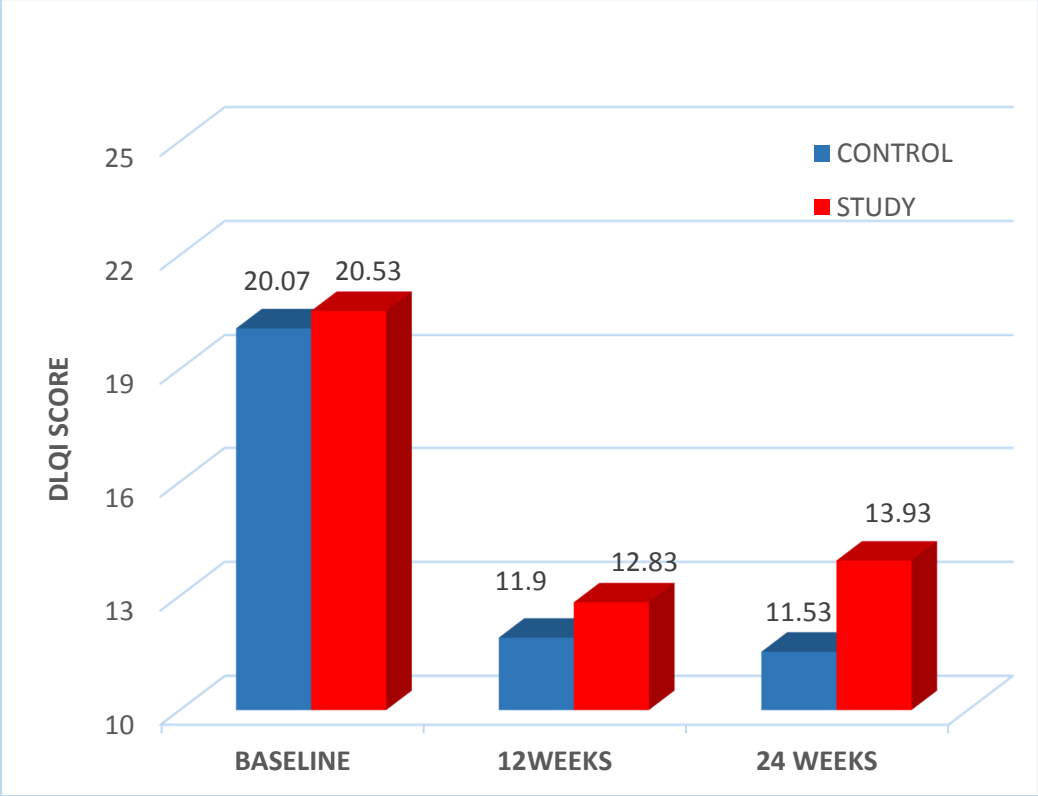


Figure 9 is a graphical representations of Table 9 and 9A.

TABLE 10: GLOBAL ASSESSMENT

DURATION	CONTROL GROUP		STUDY GROUP		P VALUE
	MEAN	S.D	MEAN	S.D	
0 WEEKS	1.57	1.14	1.37	1.07	0.49
4WEEKS	2.7	0.92	2.6	0.81	0.66
8 WEEKS	4.93	0.79	4.67	0.88	0.22
12 WEEKS	7.03	0.77	6.7	0.83	0.11
16 WEEKS	7.23	0.73	6.8	0.99	0.06
20 WEEKS	6.43	1.14	5.77	1.33	0.04
24 WEEKS	6.33	1.21	5.6	1.38	0.03
P VALUE	<0.01		<0.01		

Table-10 shows the Global Assessment score in both the control and study groups.

Within group analysis showed a significant increase in GA scores from 0 to 24 weeks in both the control and study groups. Analysis between the control and study groups showed that from 0 to 16 weeks, both the groups showed a comparable score, but at 20th week and 24th week, the control group showed a significantly better score than the study group**.**

FIGURE 10: GLOBAL ASSESSMENT

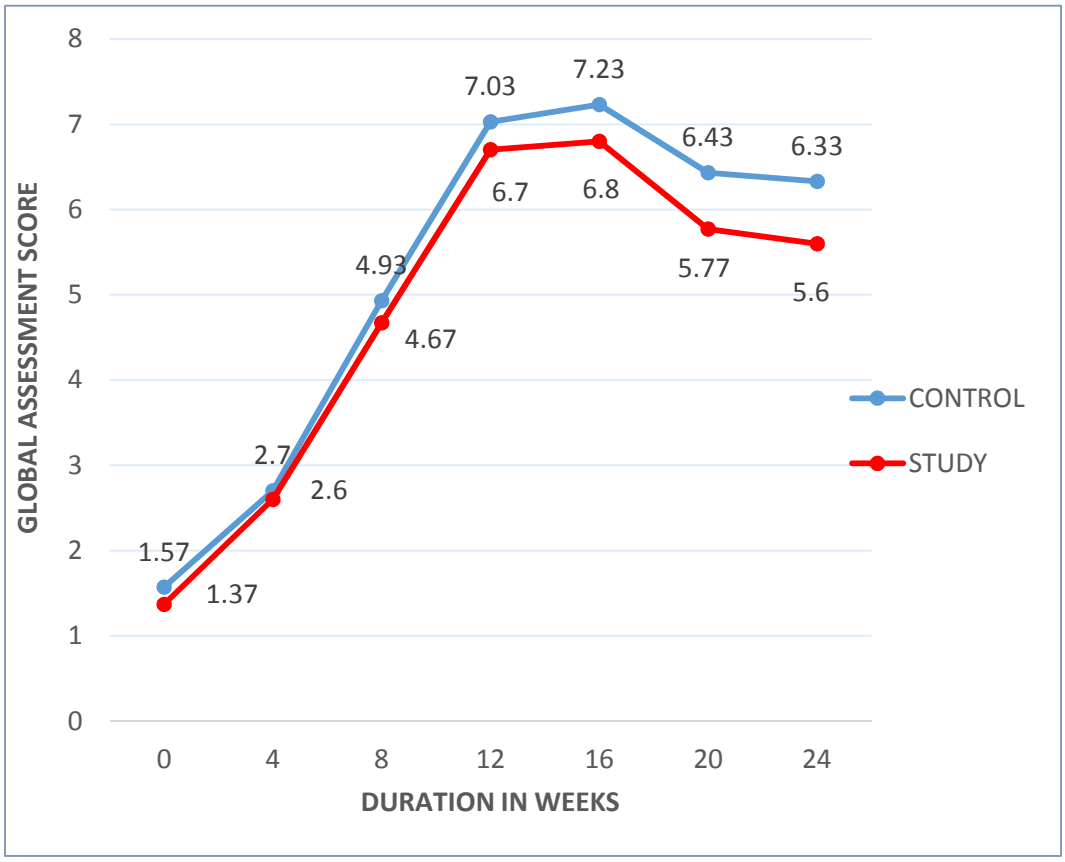


Figure 10 is a graphical representation of Table 10.

TABLE-11: GLOBAL ASSESSMENT AT 12 WEEKS

GROUPS	BASELINE		12 WEEKS		P VALUE
	MEAN	S.D	MEAN	S.D	
CONTROL	1.57	1.135	7.08	0.765	<0.01
STUDY	1.37	1.066	6.50	0.938	<0.01
P VALUE	0.485		0.019		

Table 11 shows the mean Global assessment score of control and study groups at baseline and 12 weeks. Comparison between the groups showed no difference in the mean GA scores at baseline, but at 12 weeks the control group showed a significantly higher score than the study group.

TABLE-11A: GLOBAL ASSESSMENT AT 24 WEEKS

GROUPS	BASELINE		24 WEEKS		P VALUE
	MEAN	S.D	MEAN	S.D	
CONTROL	1.57	1.135	6.33	1.213	<0.01
STUDY	1.37	1.066	5.60	1.380	<0.01
P VALUE	0.485		0.033		

Table 11A shows the Global assessment score of control and study groups at baseline and 24 weeks. Comparison reveals a lower score in the study group than the control group.

FIGURE 11: GLOBAL ASSESSMENT SCORE

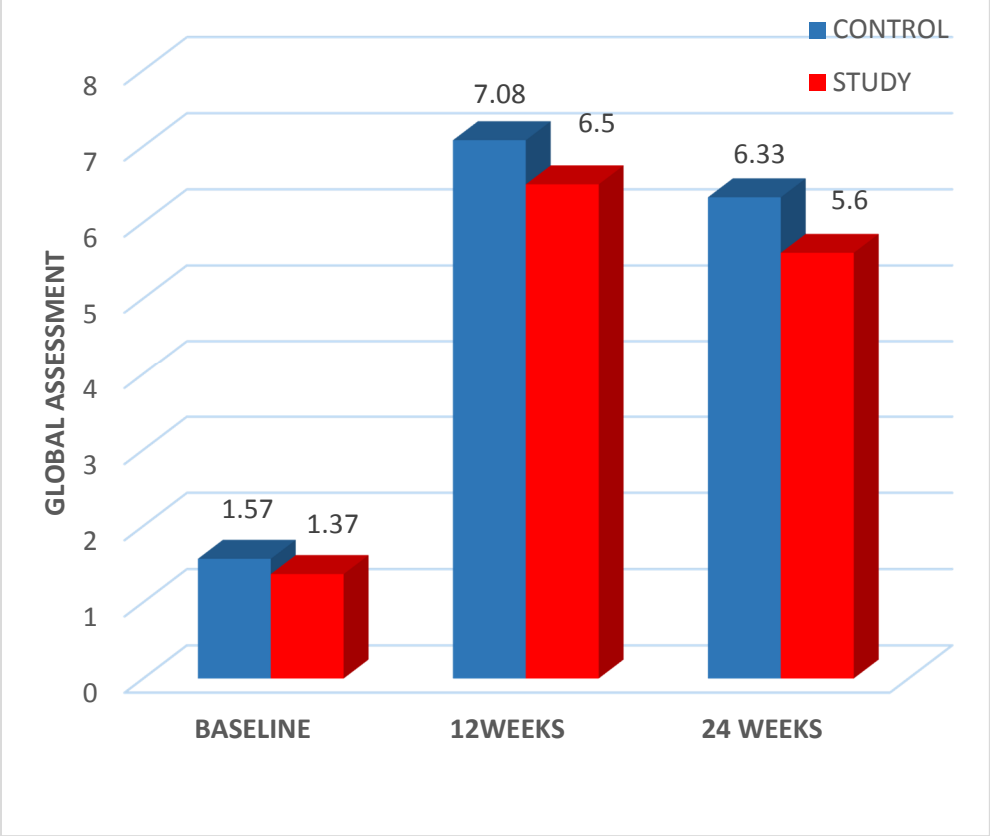


Figure 11 is a graphical representations of Tables 11 and 11A.

TABLE-11 A: LABORATORY INVESTIGATIONS (CONTROL GROUP)

INVESTIGATIONS	CONTROL GROUP		p-VALUE
	BASELINE	12 WEEKS	
HEMOGLOBIN (gm %)	11.68	11.7	0.966
TOTALWBCCOUNT (cells/mm3)	7423	7520	0.838
BLOOD SUGAR (mg/dl)	92.13	88.53	0.189
BLOOD UREA (mg/dl)	25.03	25.8	0.535
SERUM CREATININE (mg/dl)	0.98	0.94	0.33
SERUM BILIRUBIN(mg/dl)	0.89	0.82	0.12
SGOT (IU/L)	29.6	29.4	0.89
SGPT (IU/L)	28.9	29.7	0.49

Table 11A shows the mean values of laboratory investigations done in the control group at the beginning and end of the treatment period.

There was no statistically significant difference in the investigation values at baseline and 12 weeks.

TABLE-11 B: LABORATORY INVESTIGATIONS (STUDY GROUP)

INVESTIGATIONS	STUDY GROUP		p-VALUE
	BASELINE	12 WEEKS	
HEMOGLOBIN (gm %)	12.03	11.95	0.87
TOTALWBCCOUNT (cells/mm3)	7847	7070	0.11
BLOOD SUGAR (mg/dl)	91.67	88.67	0.29
BLOOD UREA (mg/dl)	24.23	25.93	0.16
SERUM CREATININE (mg/dl)	0.99	0.96	0.60
SERUM BILIRUBIN(mg/dl)	0.89	0.86	0.46
SGOT (IU/L)	29.67	29.20	0.73
SGPT (IU/L)	28.10	29.37	0.31

Table 11B shows the mean values of laboratory investigations done in the study group at the beginning and end of the treatment period.

There was no statistically significant difference in the investigation values at baseline and 12 weeks.

FIGURE 11A: HAEMOGLOBIN

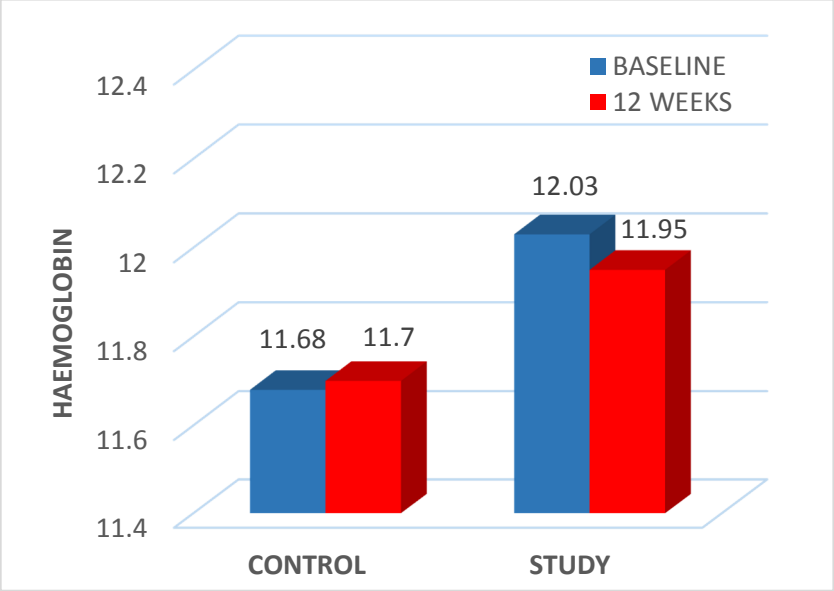


Figure-11A shows the mean haemoglobin in control and study groups at baseline and 12 weeks

FIGURE 11B: TOTAL LEUCOCYTE COUNT

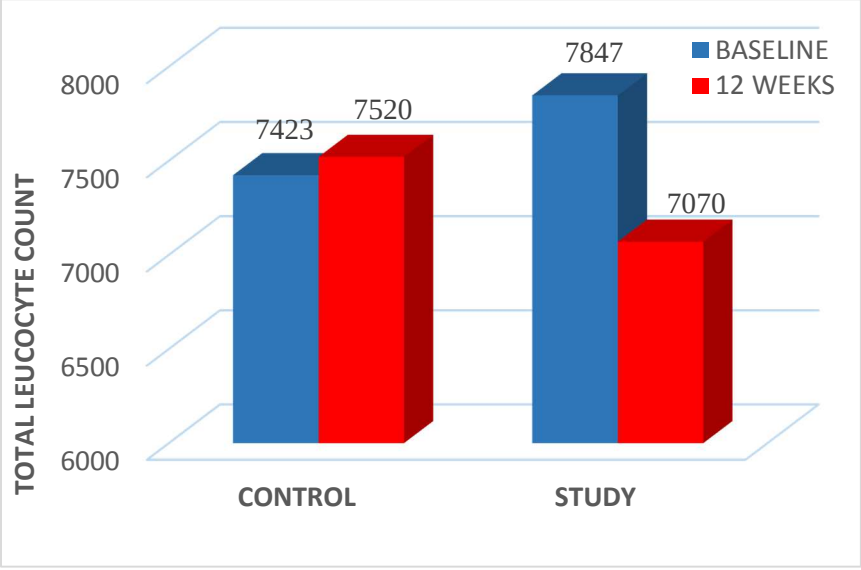


Figure-11B shows mean total WBC count in control and study groups at baseline and 12 weeks

FIGURE 11 C: BLOOD SUGAR

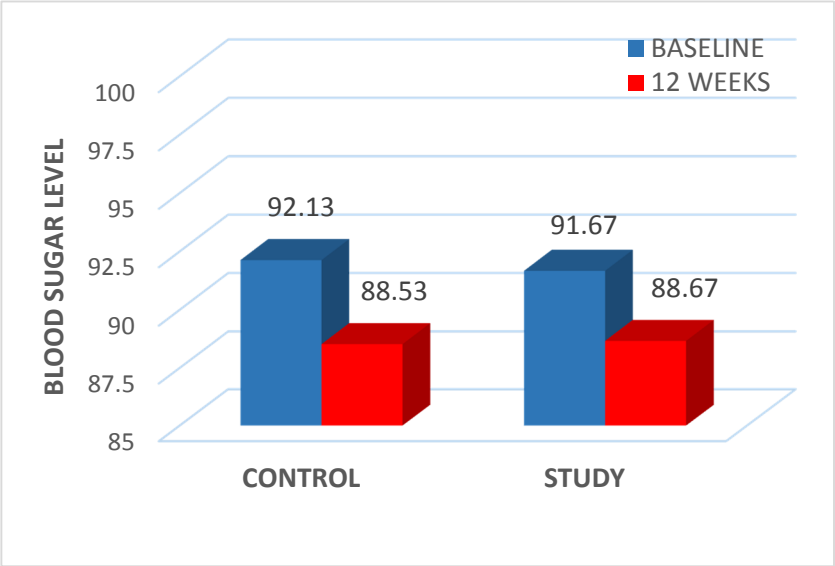


Figure-11C shows the mean blood sugar in control and study groups at baseline and 12 weeks

FIGURE 11D: BLOOD UREA

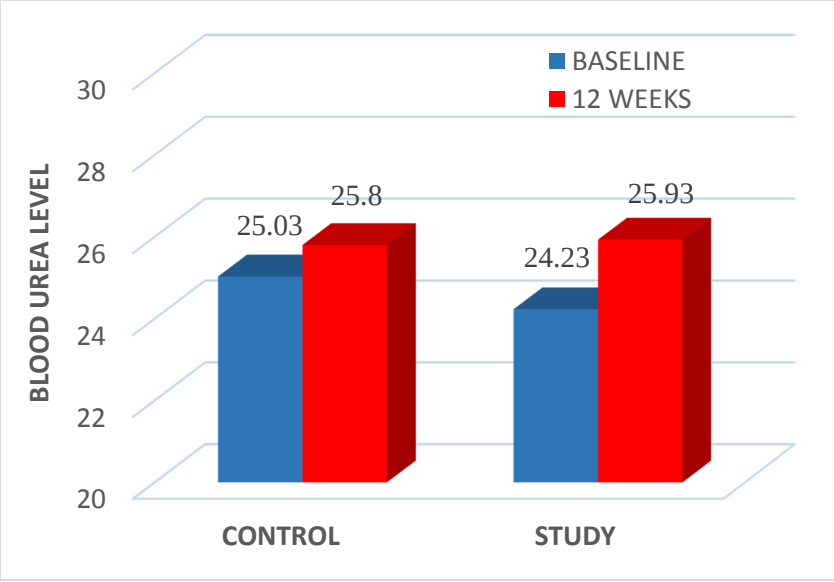


Figure-11D shows the mean blood urea in control and study groups at baseline and 12 weeks

FIGURE 11E: SERUM CREATININE

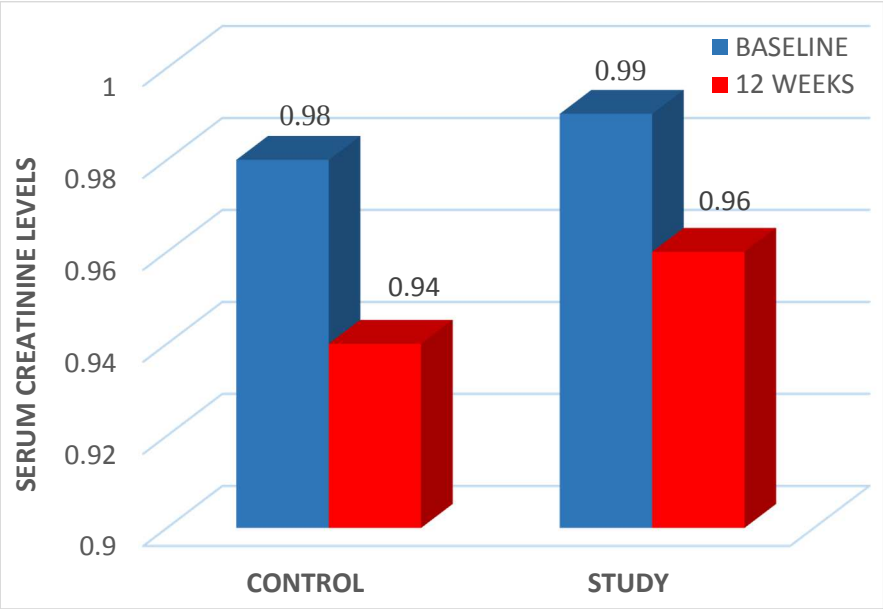


Figure-11E shows the serum creatinine in control and study groups at baseline and 12 weeks

FIGURE 11F: SERUM BILIRUBIN

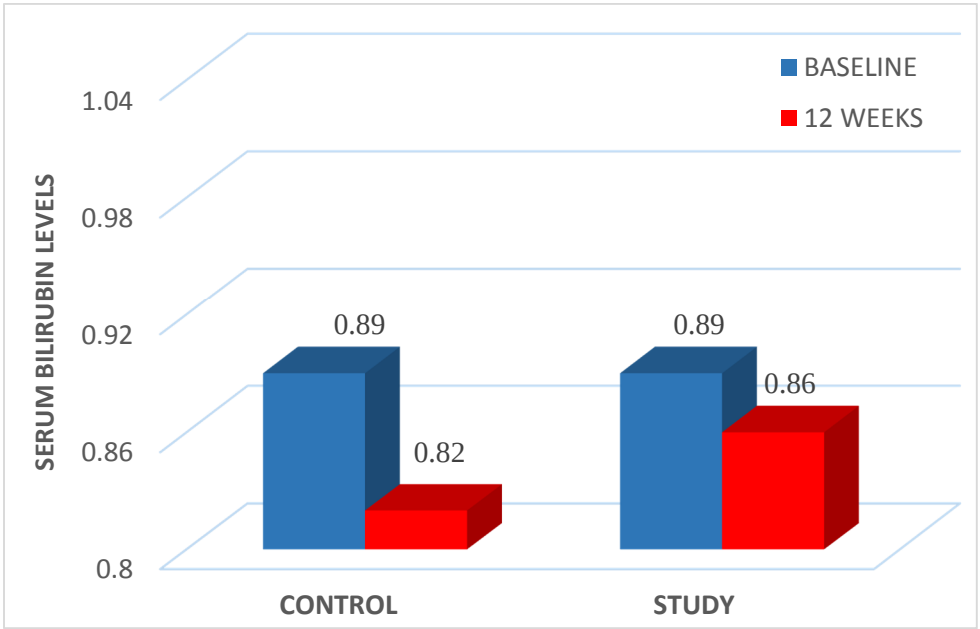


Figure-11F shows the mean Bilirubin in control and study groups at baseline and 12 weeks

FIGURE 11G: SGOT LEVELS

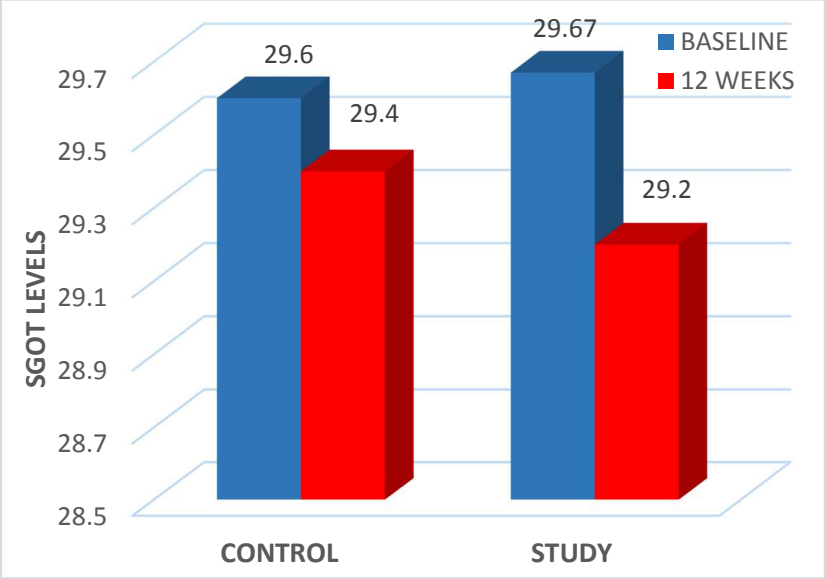


Figure-11G shows the mean SGOT in control and study groups at baseline and 12 weeks.

FIGURE 11H: SGPT LEVELS

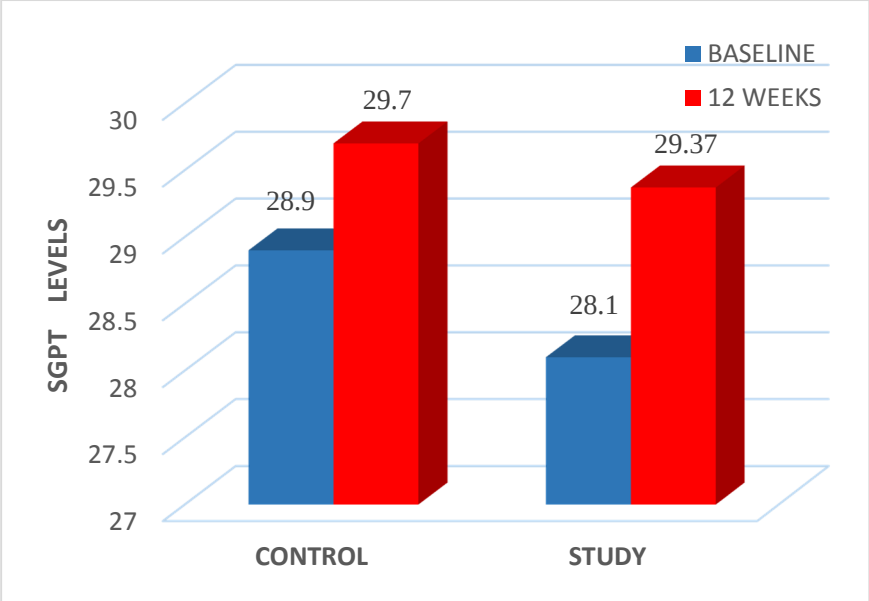


Figure-11H shows the mean SGPT in control and study groups at baseline and 12 weeks

TABLE-12: ADVERSE EVENTS

ADVERSE EVENTS	CONTROL GROUP	STUDY GROUP
NAUSEA	**1**	**2**
VOMITING	**2**	**2**
ABDOMEN PAIN	**3**	**4**
MUSCLE PAIN	**2**	**1**
HEAD ACHE	**1**	**1**
DIZZINESS	**1**	**1**

Table-12 shows the adverse events noted in both control and study groups.

Vomiting and abdomen pain were the common adverse events noted during the study.

Other adverse events noted were nausea, muscle pain, dizziness and headache.

No difference was noted in the incidence of adverse events between the two groups.

FIGURE 12: ADVERSE EVENTS

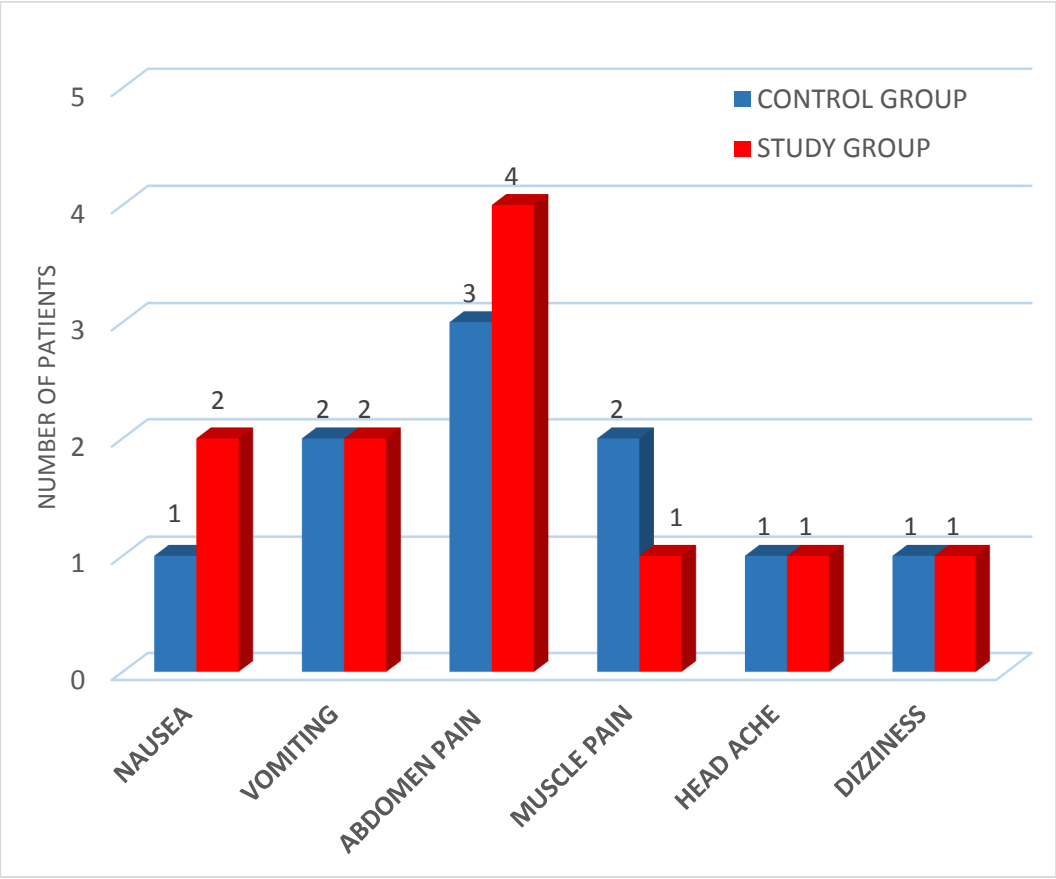


Figure 12 is a graphical representation of Table 12.

TABLE-13: RELAPSES

GROUPS	NUMBER OF PATIENTS
CONTROL	**2**
STUDY	**5**

Table 13 shows the number of patients who had a relapse.

More number of patients in study group had a relapse when compared to the control group.

FIGURE-13: RELAPSES

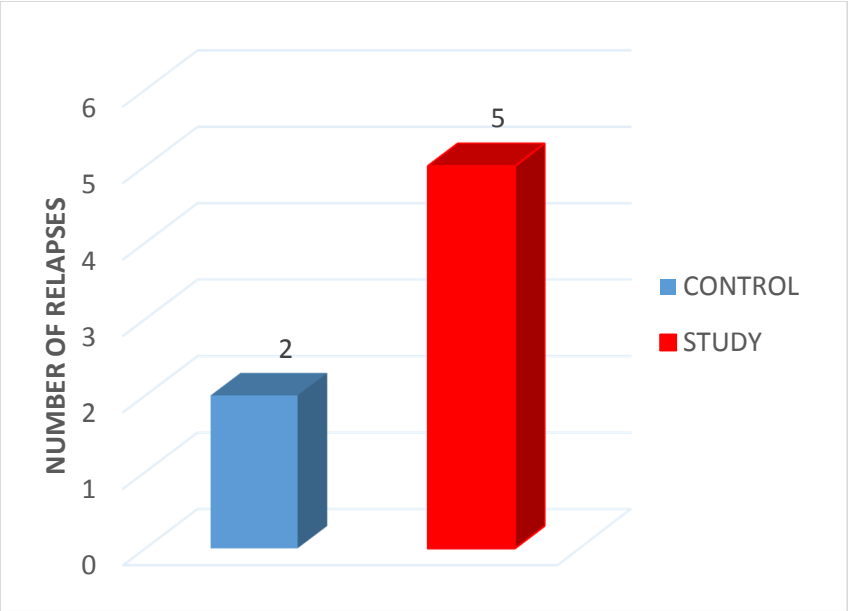


Figure 13 is a graphical representation of Table 13.

FIGURE 22A&B: TREATMENT PHOTOGRAPHS-CONTROL GROUP

Baseline

24 weeks

FIGURE 23A&B: TREATMENT PHOTOGRAPHS-STUDY GROUP

Baseline

24 weeks

DISCUSSION

DISCUSSION

Alopecia areata is a common disorder in our country. All age groups and both sexes are equally affected. Even though it is an asymptomatic condition, it causes considerable morbidity due to the cosmetic impairment. The course of the disorder is variable and prolonged. Although many topical and systemic agents are currently used, they do not offer a complete relief for the patient and may lead to distressing adverse events. Presently systemic steroids are the mainstay of treatment in a case of severe alopecia areata and administered as minipulse.

Hydroxychloroquine is an antimalarial agent which is found to have a T cell modulating action. Hence it is being used in conditions like Rheumatoid arthritis and scarring alopecias. It is also used for systemic photoprotection. Because Alopecia areata is a T cell mediated disorder, Hydroxychloroquine may offer a benefit for the patients.

This study was conducted at the Institute of Pharmacology, Madras Medical College, Chennai in collaboration with Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai. 94 patients were screened and 60 patients who fulfilled the selection criteria were enrolled for the study. They were randomized into 2 groups of 30 patients each.

Patients in the control group received a standard treatment of Tab. Betamethasone 5 mg (5 tablets of 1 mg each) on two consecutive days of the week for 12 weeks. Patients

in the study group received Tab. Hydroxychloroquine 400mg/day for a period of 12 weeks. The patients were assessed every 4 weeks using SALT score, DLQI score and Global Assessment.

Safety and tolerability of the drugs was studied by adverse events monitoring during the study period. Laboratory investigations were done at the baseline and at the end of study period. In addition, the patients were subjected to ophthalmic evaluation before and after treatment. Post treatment follow up was done for an additional period of 12 weeks. The data were collected and the results were analysed.

Basic demographic profile showed no significant difference in the mean age and sex distribution in both the control and the study groups. The average age in both the groups was 30. More number of male patients were found in both the groups. The number of patches and the mean duration of illness were also found to be comparable in both control and study groups.

In this study, the Scale of Alopecia Tool (SALT) score showed a statistically significant decrease ($p<0.01$) at the end of 12 weeks in both the control and study groups. This is in agreement with the case series of successful treatment of AA with Tab. Hydroxychloroquine. [49,50] Comparison between the groups showed that the improvement was similar in both groups during the treatment period, but in the followup period the control group treated with Betamethasone maintained the improvement. The study group receiving hydroxychloroquine did not maintain the benefits of treatment after 16 weeks.

The Dermatology Life Quality Index (DLQI) and Global Assessment (GA) scores showed changes similar to the SALT score. Both the groups of patients showed a statistically significant improvement in the Quality of Life and overall treatment response during the study period. But after stopping the treatment, both groups of patients again showed a reduction in response around 16 to 20 weeks which is more pronounced in the study group. No significant difference was noted between the groups at the baseline and end of study period.

This study shows that Tab. Hydroxychloroquine 400mg/day is efficacious in the management of patients with Alopecia areata.

No statistically significant difference in the laboratory parameters like Hemoglobin, Total WBC count, Blood Sugar, Blood Urea, Serum Creatinine, Serum SGOT, Serum SGPT is noted in the control and study groups at the end of treatment period when compared with the baseline using paired t-test. This shows that hydroxychloroquine does not affect the lab parameters and has no adverse effect on hepatic and renal functions**.**

No serious adverse events were reported in this study. Abdomen pain and Vomiting which were the most common adverse events reported by Khaitan et al for Betamethasone were also commonly noted in this study.[51]Other adverse events noted were nausea, muscle pain, dizziness and headache. The patients were asked to take the drugs after food. Other adverse events were managed symptomatically**.** No cases of retinopathy were seen in the patients treated with Hydroxychloroquine. **No significant difference in the incidence of adverse events is noted between the two groups.**

During the post treatment period, 2 patients from the Betamethasone group and 5 patients from the Hydroxychloroquine group reported with a relapse of their condition.

This study had a 12 weeks treatment period which is an insufficient time to study the course and treatment response of a chronic disease. This is an open label study and no blinding was done. The assessment parameters were more subjective and prone for observer bias. These factors may be considered as the limitations of this study.

Hydroxychloroquine 400mg/day is found to be efficacious in patients with Alopecia areata. As no serious adverse events were reported during the study period, it is concluded to be safe in these patients. Further long duration, placebo controlled and blinded clinical trials will ascertain its role and usefulness in Alopecia areata.

CONCLUSION

CONCLUSION

From this study, we conclude that,

- Hydroxychloroquine is efficacious in the management of patients with Alopecia areata.
- It can be used in those patients in whom systemic steroids are contraindicated.
- Hydroxychloroquine is well tolerated and not associated with Serious Adverse Events.

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APPENDICES

APPENDIX -I

LIST OF ABBREVIATIONS USED

AA - Alopecia areata

ANOVA - Analysis of Variance

AT - Alopecia Totalis

AU - Alopecia Universalis

DLQI - Dermatology Life Quality Index

DNCB - Di Nitro Chloro Benzene

DPCP - Diphen Cyclo Propenone

GA -Global Assessment

HFIP - Hair follicle Immune Privilege

HLA - Human Leukocyte Antigen

IRS - Inner Root Sheath

ORS -Outer Root Sheath

QOL - Quality of Life

MHC - Major Histocompatibility Complex

PUVA - Psoralens+ Ultraviolet A

SALT - Scale of Alopecia Tool

SADBE - Squaric Acid Dibutyl Ester

APPENDIX -II

A RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF HYDROXYCHLOROQUINE WITH BETAMETHASONE ORAL MINIPULSE IN THE MANAGEMENT OF PATIENTS WITH ALOPECIA AREATA.

CASE REPORT FORM

NAME: AGE/SEX : PLACE:

OP No: DIAGNOSIS:

Inclusion criteria: **YES/NO**

- Age: 18 -60 years
- Sex: Both genders
- Patients with Alopecia areata of the Scalp region.
- Patients willing to give written informed consent**.**

Exclusion criteria: **YES/NO**

- Pregnant women and lactating mothers
- Patients with known hypersensitivity to Hydroxychloroquine
- Patients with visual symptoms or evidence of retinal damage
- Those who have participated in another clinical study in the last three months
- Patients with Diabetes mellitus, Hypertension, HIV infection or any other chronic systemic illness of liver, kidney, gastrointestinal tract, heart etc.

Subject: Included/Excluded Reason if excluded:

Informed Consent Obtained: Yes/No

CONTROL/ TEST

Subject initials: Subject number:

Signature of principal investigator:

VISIT 1

1. Vitals:
2. Medical History:
3. Examination:
4. Investigations:

   Hb: Total WBC count:

   Blood sugar: Blood Urea: Serum Creatinine:

   Serum Bilirubin SGPT: SGOT:

5. Ophthalmic Examination
6. SALT score: DLQI score: GA score:

VISIT 2 (4 weeks)

1. Vitals:
2. SALT score: DLQI score: GA score:
3. Adverse Events:

VISIT 3 (8 weeks)

1. Vitals:
2. SALT score: DLQI score: GA score:
3. Adverse Events:

VISIT 4 (12 weeks)

1. Vitals
2. SALT score: DLQI score: GA score:
3. Investigations:

   Hb: Total WBC count:
   Blood sugar: Blood Urea: Serum Creatinine:
   Serum Bilirubin SGPT: SGOT:
4. Ophthalmic Examination
5. Adverse Events:

VISIT 5 (16 weeks)

1. Vitals:
2. SALT score: DLQI score: GA score:

VISIT 6 (20 WEEKS)

1. Vitals:
2. SALT score: DLQI score: GA score:

VISIT 7(24 WEEKS)

1. Vitals:
2. SALT score: DLQI score: GA score:

APPENDIX-III

PATIENT INFORMATION SHEET

Title: **A RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF HYDROXYCHLOROQUINE WITH BETAMETHASONE ORAL MINIPULSE IN THE MANAGEMENT OF PATIENTS WITH ALOPECIA AREATA.**

Investigator:

Name of Participant:

This study is conducted in Rajiv Gandhi Govt. General Hospital, Chennai. You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of this study?

Alopecia areata is a common skin problem occuring as hairloss over any part of the body. Some cases are very resistant to the available modalities of treatment. We want to test the efficacy and safety of treatment with hydroxychloroquine against betamethasone in this condition.

We have obtained permission from the Institutional Ethics Committee.

The study design

All patients in the study will be divided into 2 groups A & B. You will be assigned to either of the groups. Group A receives standard treatment & Group B receives test treatment.

Study Procedures

The study involves evaluation of improvement in your symptoms and rate of hair growth. The planned scheduled visits involve visits at 4^{th} 8^{th}, 12^{th}, 16^{th}, 20^{th}, and 24^{th} weeks after your initial visit.

At each visit, the study physician will examine you. Blood tests will be carried out twice during the study and each time about 15 ml blood will be collected. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any adverse events, you have to report it. You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.

Possible benefits to you – Hydroxychloroquine will cause regrowth of hair in alopecia areata.

Possible benefits to other people - The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc. The results of this study will be informed to you at the end of the study.

Signature of Investigator Signature of Participant

Date Date

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு :

புழுவெட்டு முடியிழப்பு (அலோபீசியா ஏரியேட்டா) நோய் சிகிச்சையில் ஹைட்ராக்சிகுளோரோகுவின் பங்கு பீட்டாமித்தசோனுடன் ஒரு ஒப்பிடுதல் ஆய்வு.

ஆய்வாளர் :

பங்கேற்பாளர் :

இந்த ஆய்வு இராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம்:

புழுவெட்டு முடியிழப்பு (அலோபீசியா ஏரியேட்டா) என்பது முடியின் வேர் கால்களுக்கு எதிராக நமது உடலின் நோய் எதிர்ப்பு அணுக்களை உற்பத்தி செய்வதால் ஏற்படக்கூடிய நோயாகும். இதன் காரணமாக உடலின் சில பகுதிகளில் முடி இழப்பு ஏற்படும். இந் நோயில் நமது நோய் எதிர்ப்பு சக்தியை மாற்றியமைக்க கூடிய இரு மருந்துகளான ஹைட்ராக்சிகுளோரோகுவின் மற்றும் பீட்டாமித்தசோன் ஆகியவைகளின் பயன் குறித்த ஒரு ஒப்பீடு ஆய்வாகும்.

இந்த ஆய்விற்கு இன்ஸ்டிட்யூசனல் எத்திக்கல் கமிட்டி சம்மதம் பெற்றிருக்கிறோம்.

இந்த ஆய்வில் கலந்து கொள்பவர்கள் **A** மற்றும் **B** என்று இரு குழுக்களாக பிரிக்கப்படுவீர். **A** குழுவில் இருப்பவர்கள் பீட்டாமித்தசோன் சிகிச்சையும் **B** குழுவில் இருப்பவர்கள் ஹைட்ராக்சிகுளோரோகுவின் சிகிச்சையும் பெறுவர்.

இந்த ஆய்வில் முதல் மற்றும் 2, 4, 6, 8, 10, 12, 16, 20 மற்றும் 24 வாரங்களில் பரிசோதிக்கப்படுவர், நோயின் தன்மையில் ஏற்படும் முன்னேற்றத்தினை அறிந்து கொள்வோம். ஆய்வின் ஆரம்பத்தில் மற்றும் 6வது மற்றும் 12வது வாரத்தில் மூன்று முறை இரத்த பரிசோதனை செய்யப்படும். அதற்காக எடுக்கப்படும் இரத்தத்தின் அளவு அதிகபட்சம் 15 மி.லி. மட்டுமே. இந்த ஆய்வினில் ஏதேனும் பக்கவிளைவுகள் ஏற்பட்டால் உடனடியாக எங்களிடம் தெரிவிக்க வேண்டும்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம். இத்தகவல் தாளில் கையெழுத்திடுவதின் மூலம் உங்களை பற்றிய குறிப்புகளோ, எடுத்து கொண்ட சிகிச்சை முறையை பற்றியோ ஆய்வாளரோ, இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியை சார்ந்தவர்களோ தேவை ஏற்பட்டால் அறிந்து கொள்ளலாம் என்று சம்மதிக்கிறீர்கள்.

இந்த ஆய்வில் பங்கேற்காவிட்டாலும் நீங்கள் வழக்கமான சிகிச்சையை தொடர்ந்து பெறலாம்.

இந்த ஆய்வில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆய்வின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆய்வாளர் கையொப்பம்

பங்கேற்பாளர் கையொப்பம்

தேதி :

APPENDIX V

INFORMED CONSENT FORM

Title: A RANDOMISED OPEN LABEL COMPARATIVE STUDY OF HYDROXYCHLOROQUINE WITH BETAMETHASONE ORAL MINIPULSE IN THE MANAGEMENT OF PATIENTS WITH ALOPECIA AREATA.

Name of the Participant:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
6. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
7. I have understand that my identity will be kept confidential if my data are publicly presented
8. I have had my questions answered to my satisfaction.
9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)
Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____ Date_____
Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:
Name _____ Signature_____ Date_____

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு :

புழுவெட்டு முடியிழப்பு (அலோபீசியா ஏரியேட்டா) நோய் சிகிச்சையில் ஹைட்ராக்சிகுளோரோகுவின் பங்கு பீட்டாமித்தசோனுடன் ஒரு ஒப்பிடுதல் ஆய்வு.

பெயர் : வயது : தேதி : வெளிநோயாளி எண்:

..... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக அறிந்து கொண்டேன். எனது சந்தேங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன். இச் சுய ஒப்புதல் படிவத்தை பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை பற்றி அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என் சம்மதிக்கிறேன்.

இந்த ஆய்வின் முடிவுகளை வெளியிடும்போது எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன். இந்த ஆய்விற்காக இரத்தப் பரிசோதனை செய்துக் கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன் என்று புரிந்து கொண்டேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்து கொண்டேன்.

பங்கேற்பாளர் கையொப்பம் தேதி :

ஆய்வாளர் கையொப்பம் தேதி :

DERMATOLOGY LIFE QUALITY INDEX

Hospital No:
Name:
Address:

Date:

Diagnosis:

DLQI Score: ☐

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes ☐ No ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. J.Jeyasudha,
Postgraduate MD (Pharmacology),
Madras Medical College,
Chennai – 600 003.

Dear Dr. J.Jeyasudha,

The Institutional Ethics Committee has considered your request and approved your study titled **A Randomized, open label comparative study of Hydroxychloroquine with Betamethasone oral minipulse in the management of patients with Alopecia areata. No.50082014.**

The following members of Ethics Committee were present in the meeting held on 05.08.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandhini, M.D., Inst.of Pharmacology, MMC	: Member
5. Dr.G.Muralidharan, Director Incharge, Inst.of Surgery	: Member
6. Prof.K.Ramadevi, Director i/c, Inst.of Biochemistry, MMC	: Member
7. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
8. Prof.Tito, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
9. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
10. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
11. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003